The American Heart Journal

VOL. 17 JUNE, 1939 No. 6

Original Communications

THE SOUNDS PRODUCED BY THE FRICTION OF NORMAL SEROSAE*

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FOR a century, since the pioneer contribution of Laënnec,[1] auscultation has been studied assiduously by physicists, physiologists, and clinicians, yet there are many acoustic phenomena whose significance has not been determined. The cardiac sounds and the adventitious cardiovascular sounds are not yet fully understood and offer, therefore, obvious difficulties in diagnosis.

Empirically, we have succeeded in identifying the clinical significance of many acoustic phenomena, but daily practice demonstrates the insufficient pathogenic value accorded to other phenomena not less frequent or important. Mackenzie[2] stated correctly, "How little we know of the causation of murmurs," and Wiggers, when dealing with the cardiac sounds, explains the mechanism of the first one merely in terms of probability. The clinical investigators have avoided academic discussions and attempted to establish the value of the acoustic data on the basis of the pathologic findings; but it is frequently impossible to obtain pathologic control, and the necropsy findings often contradict the clinical data. The complexities of the problem are shown by the numberless hypotheses accumulated by clinicians during a hundred years of auscultation; on the other hand, the contemporary literature bears testimony to the hope of finding a definite reason for the disparity between the physical phenomena and the functional evolution. Pathologic physiology may bring certainty to prognosis and therapeutics.

A glance at the appendix of White's book, *Heart Disease,* which includes representative examples of "the more important or puzzling problems in cardiovascular diagnosis," justifies any contribution to the subject.

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Received for publication Sept. 3, 1938.

The present study deals with the acoustic phenomena which occur when there is friction of two serosae in the pericardium, pleura, or peritoneum. The source of these sounds is really in the membranes or structures covered by endothelium when interserous friction occurs. The purpose of this study was not only to review the classical auscultatory findings in cases of nonglistening, diseased, or inflamed serosae, but also to investigate the possibility of the appearance of sounds in normal serosae lubricated by the physiologic transudates.

Semeiological investigations of this problem have been made frequently since Laënnec. The opinions derived therefrom are practically unanimous: both the older and contemporary clinicians agree that intact serosae are aphonic, or silent. Laënnec himself, however, and several other observers have expressed suspicions that this proposition may have limitations.[3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] Some authors have favored the view that minimal lesions of the endothelium or insignificant alterations in their lubrication might be responsible for some of the acoustic phenomena present in apparently healthy individuals. Nevertheless, they did not conclude that perfectly normal serosae, with a physiologic lubrication, can yield acoustic phenomena useful in clinical work. Indeed, such a conclusion cannot be legitimately derived from their experiments or observations because of the lack of adequate controls.

This problem, apparently only speculative in nature, is in reality intimately bound up with the validity of auscultatory data. It may be approached experimentally, and hence supply conclusions of interest especially for cardiologic pathology and semeiology.

METHODS

Normal, healthy cats, rabbits, and dogs were used. This material eliminates, therefore, possible objections as regards the integrity of the serosae. The animals were killed by excessive anesthesia, by hemorrhage, or by asphyxia. Several fragments of the thoracic and abdominal walls and also several viscera (heart, liver, spleen, intestine) were collected.

The lubricating fluids were water, normal saline, Ringer's solution, oxalated or saturated blood, blood plasma or blood serum, and saliva, all from the same animal. The normal transudates from the serosae might also be employed; it is difficult, however, to collect them. The inevitable evaporation which occurs renders the serosae sticky; it was therefore invariably necessary to employ the other lubricating agents mentioned. Furthermore, the handling of the pieces during their preparation might leave microscopic foreign bodies on the endothelium. For this reason, all the structures employed were always washed first with some of the fluids mentioned.

Binaural stethoscopes and phonendoscopes were used, of the type commonly employed in clinical work. The receptors were of several forms: bells, cones, diaphragms, small funnels, or glass cylinders.

Some observations were made by applying a crystal microphone to the fragment of thoracic or abdominal wall, and leading the electrical waves thus produced through an amplifier into a cathode-ray oscillograph and a loud-speaker. The sounds could then be seen on the face of the cathode-ray oscillograph tube or heard from the loud-speaker by several observers. Since the electrical records

of complex auditory phenomena do not furnish any information as to the acoustic characteristics of the sounds, and since measurement of the intensity of the sounds recorded is an elaborate process and can only be performed in an indirect manner, no graphic records are presented of the observations made in this way. Such observations, however, fully confirmed those obtained directly.

The sounds heard under the conditions to be reported were frequently listened to by independent observers. No discrepancies of opinion occurred.

Many different preparations may be made with the thoracic or abdominal walls. A few of the most commonly used will be mentioned.

1. Removal of the thoracic skin; opening of the thoracic cavity in the midline; separation of the mediastinum to one side or total extirpation of it; wide opening of the thoracic cavity by means of hooks or clamps attached to the animal board; application of the receptor of the stethoscope on the outside surface of one hemithorax, fixing it by means of an adequate clamp; cleaning of the parietal pleura with normal saline to remove the blood, hairs, etc., which may have been deposited during the previous maneuvers and might not be recognized macroscopically; friction of the pleura with the isolated heart, spleen, or one of the small lobes of the liver at the region underlying the receptor. These organs were extracted and preserved with all the precautions necessary to avoid damage to their endothelial lining and to eliminate foreign bodies.

2. Removal of the thoracic skin; section of the ribs on both sides of the spinal column, thus obtaining a fragment which comprises the costal and sternal regions (the section at the neck and abdomen need not be described); fixation of the sternocostal fragment over a stethoscopic receiver by means of clamps and stands.

When producing friction in this preparation, the midline should be avoided because of the remnants of the retrosternal section of the mediastinum (mesopericardiac ligament, Ranvier[14]). Two types of experiment may be performed with this preparation: (1) A receiver is placed on one of the hemithoraces distal from the sternum. Friction is exerted on the inside over the ribs and intercostal spaces. (2) The receiver is fixed similarly. The fragment is then bent, using the chondrosternal joint on the same side as a hinge, so that these joints become prominent. Then a firm organ is rubbed against these joints. A bent hepatic lobe or fragment of left ventricular wall may be used. The possibility of bleeding or oozing should be kept in mind, and, if necessary, the preparation should be washed with normal saline. Here again, the attachment of the mediastinum should be avoided.

3. Removal of the thoracic skin; separation of a hemithorax by section of the ribs at the spinal column and near the sternum; holding this fanlike fragment with two large clamps placed in a direction parallel to the ribs at the ends; fixation of the preparation on stands so that by tension exerted on the handles of the clamps by means of rubber bands it is possible to distend the intercostal spaces at will. The placing of the stethoscope and the friction are performed as in the previous cases.

4. Removal of the abdominal skin; extirpation of the abdominal wall by cutting along the pelvic, thoracic, and vertebral insertions. This rhomboidal fragment can be utilized as a whole or in part. On one side it is fixed firmly by means of a large clamp, and to the other side a clip is attached on which variable weights may be applied. The receiver is placed underneath the tense horizontal membrane. The peritoneum is rubbed as in the previous examples, or else by means of any solid body covered with another abdominal fragment.

5. A piece of abdominal wall is tied to the base of a glass cylinder 5 cm. in diameter. Variable pressures may be exerted by means of a manometer. The receiver of the stethoscope is similarly covered by abdominal wall with its peritoneum. When the friction is made, it will occur only on a very small area,

because of the convexity of the tissues on the glass cylinder. The small size of the area of contact is further controlled by looking at the preparation tangentially against a light. Movements of the receiver can be made by hand or by means of silent movable stands.

These five preparations may be combined in countless ways. The abdominal viscera, especially, may be used in a wide variety of ways.

The physiologic state of the serosae and lubricating fluids can be readily changed so as to reproduce the clinical phenomena. The effect of drying, roughening, and interposition of clots of blood or lycopodium powder can be studied under fully controlled conditions.

In another series of observations the two following preparations were used:

6. Opening of the left ventricle of a large dog; fixation of the receiver in different parts of the surface of the ventricle; friction between the endocardium and different test objects (chordae tendineae, cusps, etc.) in several places.

7. Removal of the heart of a large dog after previous ligature of the vessels; further distention of the right auricle and ventricle by injection of water through one of the cavae; application of the stethoscope to the apex; and friction at different points, mainly at the posterior wall of the right auricle.

RESULTS

It appears unnecessary to report in detail the observations made under the several experimental conditions described. The following general statements summarize the results with all the preparations tested.

1. In all the normal serosae, noises and sounds will be caused by sliding when they are really in contact. If the lubricating fluids prevent their contact, no sound may be heard.

2. The tension of the subendothelial membranes and the hardness of the organs covered by the serosae are the two factors indispensable for the force of attrition to make the contact possible.

3. Normal serosae adequately lubricated (by normal saline, Ringer's solution, oxalated blood, blood plasma, blood serum) yield noises and sounds which depend on the elasticity of the structures covered by the serosae.

4. These elastic vibrations appear as noises of countless qualities and sounds of diverse loudnesses, pitches, and qualities.

5. All kinds of murmurs may be reproduced by the friction of structures covered with normal endothelium: soft, blowing, scraping, squeaking, musical, etc. All the intermediate varieties of dry murmur and typical friction rub can also be obtained.

6. All kinds of murmurs and friction rubs may also be obtained by the attrition of structures in which the endothelial lining is abnormal or absent.

7. The typical friction rubs are produced more readily by separating the structures in contact than by sliding.

8. Friction rubs may be reproduced by interposition of foreign bodies between normal serosae, e.g., clots of blood, lycopodium powder, etc.

9. All the noises mentioned may be transmitted for long distances. Friction at the posterior wall of the right auricle is clearly heard at the

apex (observation 7) even when the movement of the surfaces in contact is only a few millimeters.

10. A typical friction rub may be transmitted with the acoustic characteristics of a blowing murmur.

11. Acoustic manifestations are greater when the friction is exerted along an axis perpendicular to the direction of the muscular, tendinous, and elastic fibers or of the subendothelial irregularities, other conditions being equal.

No acoustic or tactile vibrations are produced by the sliding of structures covered with endothelium when the sliding is indirect, i.e., when the surfaces are separated by a lubricating fluid and the pressure is slight.

DISCUSSION

Before analyzing the practical importance of the data reported, it is pertinent to review briefly some of the physical principles related to the subject.

As is well known, acoustics is a chapter in the theory of elasticity (see any standard textbook of physics).

Four types of solid bodies are specially considered in acoustics: strings, rods, membranes, and plates. Sound is the result of rapid oscillations of elastic bodies. These vibrations are produced by plucking, percussion, or friction.

Transversal vibrations of strings are produced by friction, as in the violin; by striking, as in the piano; by plucking, as in the harp. The characteristics of these vibrations depend on the length, the thickness, the tension, and the density of the string. Longitudinal vibrations yield higher-pitched sounds than those produced by transversal vibrations. The tension of the string has no influence on the frequency of the longitudinal vibrations.

Vibrations of membranes are produced by the same factors which influence strings. The sound obtained is higher-pitched when the area decreases or the tension increases, under equal conditions of thickness and density. In uniform plane membranes with constant density, the frequencies of the fundamental tones vary with the shape, even though the area remains unchanged.

Friction is caused by the minute irregularities of the surfaces of solid bodies. These irregularities are always present, even on the smoothest surface. The possibility of obtaining friction implies a certain compressibility of the solids employed. Whether the surface asperities will be crushed, broken, or elastically deformed during friction depends on the nature of the bodies concerned. "The force of friction" is the force tangential to the contact surfaces which opposes the relative movement of the solids studied. Surfaces of the same nature offer a greater resistance to friction than those of different nature, because the size and pattern of their irregularities are similar and a better fit is therefore obtained.

Static friction, or friction of adherence, is that which occurs between adjacent quiet bodies. Kinetic friction is that which occurs during movement. Indirect friction is that which appears between lubricated bodies. The variable resistance to movement, or coefficient of friction, is not a constant quantity, but a value which depends on several factors. The laws of Coulomb, Hirn, and Petroff may be summarized as follows as regards their applicability to the present problem:

(1) The coefficient of friction is proportional to pressure; (2) it depends on the nature of the bodies and the state of their surfaces; (3) it is independent of the area of the surfaces of contact, other conditions being equal; (4) when a movement is started it is independent of the speed; (5) when the compressible bodies have been in contact for some time, the coefficient is greater when the movement is started than during the movement (this difference is negligible for hard bodies); (6) the coefficient is inversely proportional to the depth of the coat of lubricating fluids in indirect frictions.

It may finally be mentioned that the elastic vibrations originated by sliding or friction may be appreciated acoustically or by touch.

The experimental data reported in the present study may be divided into two categories: (1) Noises produced by direct friction of normal serosae; (2) noises originated by direct friction of abnormal serosae. There is no fundamental difference between normal and abnormal serosae from the standpoint of the acoustic phenomena engendered by friction. The sounds obtained in either case are indistinguishable. They appear in identical conditions. The only factors of importance in the production of the elastic vibrations which originate the acoustic phenomena are the efficient tension or hardness of the underlying structures and the variable force of friction which brings their elasticity into action.

It is important to emphasize that the sounds observed, even those which occur when the bodies in contact are separated, do not occur in the endothelium but in the subendothelial structures. The efficient cause is the physical property of these structures; the determining cause is the force of friction; and the adjuvant causes are the qualities of the endothelial lining and of the interposed fluid or solid substances. Since the efficient cause is always the same, the uniformity of the acoustic phenomena is readily understood. The multiplicity and mutability of these acoustic manifestations are a consequence of the variations in the subendothelial elasticity and of the indefinite number of combinations between the determining and adjuvant factors. The transmission of these phenomena is but a special aspect of the general subject of propagation of sound and need not be considered here.

Is it possible that normal individuals generate noises due to the physiologic sliding of serosae?

This possibility cannot be denied *a priori*, because, physiologically, pressures exist which are capable of engendering direct frictions.* In the experimental study quite intense sounds appeared when the pressure between the normal membranes was no greater than 2 cm. of mercury. It may therefore be concluded that the pressures which exist in some of the mediastinal organs are sufficient to produce direct friction between structures which anatomically and functionally fulfill the experimental conditions.

Do such acoustic phenomena, similar to the sounds produced experimentally, actually occur in the normal individual? If they do, can they be explained by the friction of serosae? It is well known that such acoustic phenomena are audible in healthy individuals. These physiologic sounds vary considerably. Although some of them cannot be described precisely, they may be classified into two general groups: murmurs and friction rubs. Functional (physiologic), transitory, and inorganic murmurs over the precordial region are very frequent. The physiologists and clinicians are familiar with them. Proteiform noises which do not have the characteristics of murmurs are not so well known.[5, 8, 15, 16]

Other similar observations cannot properly be judged as applicable to normal individuals.[4, 7, 9, 11, 12, 17-50]

The next question to be answered is whether these physiologic sounds and those which appear in normal endothelia, in subjects who are not otherwise normal, can be accounted for by the observations reported here. It is generally admitted that these acoustic phenomena are due to the elastic vibrations of structures in the mediastinum. Since direct friction is a known cause of vibration, it is reasonable to attribute them to interserous friction when the conditions pointed out are fulfilled.

It may be stressed again that the friction of normal endothelium produces experimentally all the acoustic manifestations mentioned and that the sliding of abnormal endothelium of serosae likewise sets up audible vibrations. The conditions in which both these sets of acoustic phenomena can be reproduced throw light upon two very important problems of cardiology and physical diagnosis of the thorax: (a) contradictions between the clinical picture and the post-mortem findings; (b) contradictions between the physical signs and the functional disturbances. These surprising and numerous contradictions clearly denote the inability of the classical theories to cope with all the problems of auscultation. The data presented complement these classical theories and account for these hitherto puzzling problems. The form, location, and size of the organs, and also the tension and friction forces which occur at the heart, the pericardium, and the pleurae in the normal subject and in cases of thoracic disease afford a logical basis for fruitful analysis

*Direct friction occurs when there is a lubricating fluid, if the force applied is sufficient to displace it.

of all the obscure problems of auscultatory semeiology. The fact that not all normal hearts present murmurs and friction rubs does not invalidate the preceding conclusions. In the first place, the conditions for the appearance of these sounds are several; if one of them should be lacking, the sounds would not occur. Furthermore, the heart sounds will interfere in circumstances so obvious that it is not necessary to mention them; they may mask, change, or re-enforce the acoustic manifestations due to friction. A similar argument applies to the cases in which obvious lesions in the serosae of the heart and surrounding structures do not lead to the appearance of the expected rubbing sounds.

A few clinical instances selected at random will now be analyzed in the light of the present study, for illustrative purposes.

1. *Pericardial Processes (pericarditis, infarcts, "milk spots").*—The murmurs of evident pericarditis, with no demonstrable manifestations in the cardiac muscle or valvular systems, their topographical and chronological instability, their changes into friction rubs, can all be explained on the basis of the murmurs of serous origin. This statement does not imply a negation of the possibility of adventitious noises appearing according to the classical theory of fluid eddy currents, when it is possible to prove clinically that the necessary conditions are present. The statement of Soulier,[13] although contradicted by Potain, is correct, that murmurs may appear in pericarditis when the endothelium is altered, and that murmurs may also appear when this alteration is not of inflammatory origin. The murmurs which precede the rubs caused by myocardial infarction and those which persist[51] during its evolution, with the characteristics described by Castex,[52] can also be due to the serous frictions. A post-mortem examination of pieces of infarct and repetition of the experiments 6 and 7, described previously, will necessarily suggest that some of the pericardial sounds are similar to those reproduced in the laboratory. The thesis that "milk spots"[6, 53] are a source of adventitious sounds, although the surface is smooth, is supported by the present evidence. It is likely that other equally slight pericardial alterations will produce similar effects.[54-67]

2. *The Endocardial Processes (without demonstrable valve lesions or anomalies in the capacity of the cavities).*—The region of the heart where most intense friction may occur is obviously the left ventricle, and roughening of the lining is frequent in this region. The possibility that sounds may be set up by frictions in this cavity cannot be denied even when the pathologic changes are minimal.[6, 68-80] Especially during the silence of diastole, the clinician may interpret many adventitious sounds as due to serous frictions. The structure of the mitral valve, its fineness,[81] its tension during systole, the localization and histologic situation of the tiny vegetations in some varieties and periods of endocarditis suggest the possibility that certain merosystolic and holosystolic murmurs may be due to vibrations from serous frictions, similar to those produced

by liquid currents. If it is accepted that murmurs of liquid-current origin are produced by transversal vibrations,[53, 69, 82, 83] then the conclusion cannot be avoided that such vibrations may be set up by friction (the vibrating structures are practically a conglomerate of tense strings), regardless of what physiologic theory is adopted to explain the closure of the orifice. What was stated previously for accidental and inorganic murmurs may apply to the present phenomena. Why should the clinician insist on limiting his hypothesis to the theory of eddy currents in the cases in which the roentgenograms demonstrate a normal heart and there are no signs of any hydraulic disturbance?

3. *The Extracardiac Processes.*—The methodical critique which Tripier and Devic[16] have made of the theory suggested by Laënnec[1] and later developed by Potain,[84] on the role of the lung borders overlapping the heart, has not been adequately answered. The data summarized by Fahr[85] also cast doubt on Laënnec's theory. The interpretation adopted here for murmurs of serous origin may extend to all acoustic phenomena in the mediastinum when the lesions which the classical theories require cannot be demonstrated satisfactorily.[86-112]

SUMMARY

The acoustic phenomena produced by friction of organs covered by normal and abnormal serosae, lubricated by normal and abnormal fluids, were studied in rabbits, cats, and dogs.

Direct friction of structures covered by normal endothelium, lubricated by normal, physiologic fluids, is a source of murmurs and friction rubs.

Direct friction of structures covered by abnormal serosae is also a source of murmurs and friction rubs.

The importance of these data for the correlation of clinical, pathologic, and post-mortem findings is discussed.

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ELECTROCARDIOGRAPHIC RESPONSE TO GRADUALLY INDUCED OXYGEN DEFICIENCY

I. Response of Normal Hearts in Various Age Groups

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IT HAS been known for a long time that induced oxygen deficiency produces striking changes in the electrocardiogram of the human heart. In order to determine the significance of these changes, the degree of correlation between progressive deficiency of oxygen and variation in the electrocardiogram in people with normal hearts in various age groups, and in persons with diseased hearts, as well, has been studied. Whereas this publication is concerned mainly with the reaction of normal hearts, subsequent publications will deal with various groups of patients with heart disease.

REVIEW OF LITERATURE

The first experiments with induced anoxemia were made by Greene and Gilbert, in 1919.[1] They studied and described the specific changes in the electrocardiographic curves in anoxemia produced by the rebreathing method. When Rothschild and Kissin,[2] who concluded from similar experiments that anoxemia is in part responsible for pain in angina pectoris, studied the electrocardiographic changes, they found them more frequently in patients with angina pectoris than in patients without coronary disease.[3] In their study, however, only two normal, healthy subjects were tested. Katz, Hamburger, and Schutz[4] observed and described the effect of generalized anoxemia on the electrocardiogram of normal subjects. They recorded changes similar to those produced in people suffering from anginal pain. Levy, Barach, and Bruenn,[5] using a special apparatus which kept the oxygen content of the inspired air constantly at 12 per cent, took electrocardiograms of persons with, and without, cardiac disease. In both groups the typical changes in the form of the electrocardiogram were observed also, but in those with normal hearts they were found to be of minor degree.

Elaborate studies regarding breathing mechanism, blood pressure, degree of oxygen diminution in the expired air,[1-5] as well as circulation time, venous pressure, and blood oxygen saturation[5] have been made during the stages of anoxemia. The final oxygen concentration in the expired air varied from 13.5 per cent to 6 per cent. Within this range, neither the onset of discomfort nor the degree of electrocardiographic change seemed to follow closely the decrease of oxygen in the expired air at the end of the test. In studying two normal subjects, Rothschild and Kissin found that one developed S-T changes when the oxygen con-

Received for publication Nov. 7, 1938.

tent of the exhaled air at the end of the test was 8.1 per cent, and that the other did not show any change when it was 6.1 per cent. No striking difference with respect to their ability to tolerate oxygen want was found among the young and older normal subjects and patients with heart disease.

In none of the investigations was the age of the tested subjects given.

METHODS

For inducing gradually increasing anoxemia, a rebreathing method similar to that already used by Greene and Gilbert[1] was employed. The subject was connected to a Leitz basal metabolism machine (Fig. 1) filled with room air. The carbon dioxide was removed in the usual way by soda lime. The rebreathing curve was recorded, as in measuring the basal metabolic rate, in order to study the respiratory mechanism during the progressive stages of anoxemia. Before, during, and at approximately three minutes after the test, electrocardiographic records were taken. Only the three standard leads were used because the direct lead did not seem to add anything of importance to the results.

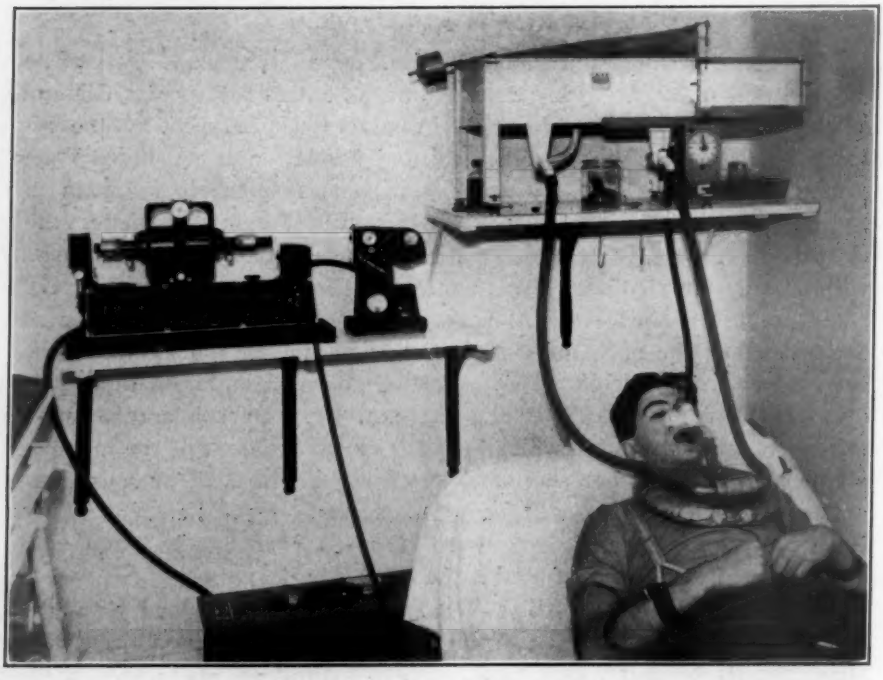

Fig. 1.—Method.

The patient was placed on a comfortable couch, and was told that he might expect some slight discomfort after several minutes of rebreathing, and to raise his arm when the discomfort made him uneasy. He was carefully watched during the test for any signs of cyanosis or dyspnea. When the patient raised his arm, or if dyspnea or cyanosis became severe, the test was stopped. The duration of the test ranged from seven to fourteen minutes and was approximately the same in both normal subjects and patients with heart disease.

Because the time necessary to record an electrocardiogram was from thirty to forty-five seconds, the time given in the legends coincides as nearly as possible with Lead II. Since the last tracing was taken as near the end of the period of anoxemia as possible, Lead III is sometimes disturbed by unrest or by removing the mouth piece and nose clamp.

RESULTS

Fifty individuals whose hearts were thought to be normal, as judged by means of physical, roentgenologic, and electrocardiographic examinations, were tested. When these individuals are arranged according to age, there are found to be ten in the group between fifteen and twenty years, ten in each of the decades from twenty to fifty, and ten between the ages of fifty and seventy. Descriptions of the several age groups, together with illustrative examples in each, follow.

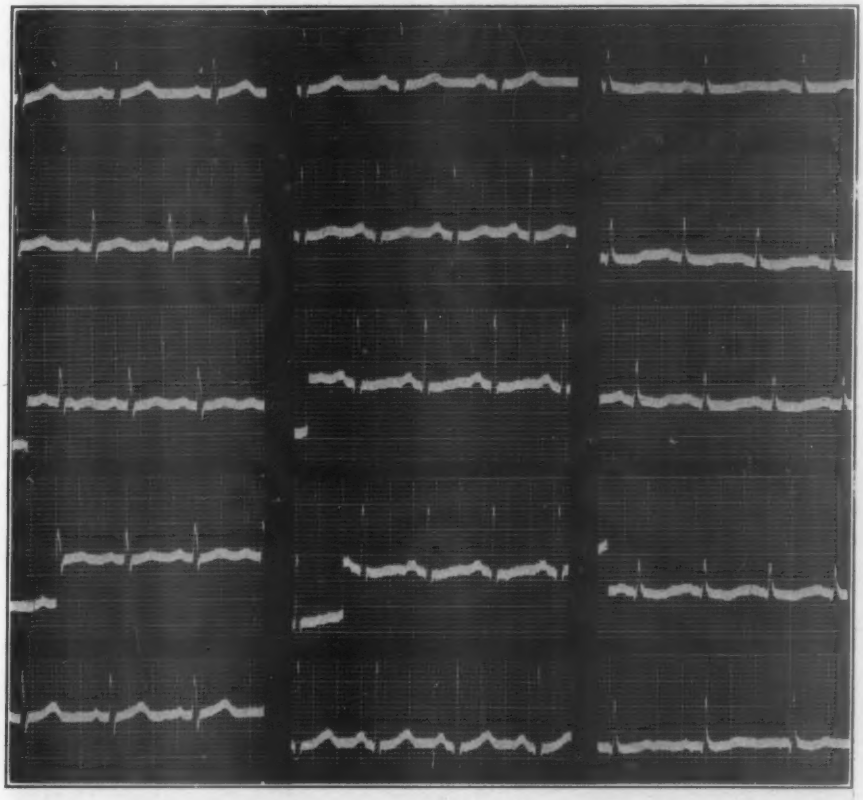

Fig. 2.—F. T. Age, 18. Normal heart. Very athletic. Test: 7 min. Discontinued because of shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 2, 4, and 6½ minutes after beginning to rebreathe. Last record, after 2 minutes of breathing room air.

1. (15 to 20 years.) In this group, four tests showed complete eradication of the T wave (Figs. 2 and 3) in Lead II; four, reduction of the T wave to considerably less than half its original height; and two, a smaller reduction. The subjects whose T waves were eradicated are

very active young people who are athletic and accustomed to competitive sports. The two subjects who showed the most moderate diminution of T_2 are asthenic in type and are unaccustomed to bodily exercise.

2. (20 to 30 years.) This group showed, in general, slightly less change in the electrocardiograms taken during the test than the previous one. There was only one record in which T_2 was abolished (Fig. 4), and there were three in which it was reduced to less than half its original height. The other six records show a very considerable reduction of the height of the T wave (Fig. 5). As before, there was an obvious correlation between the degree of change and the amount of bodily activity.

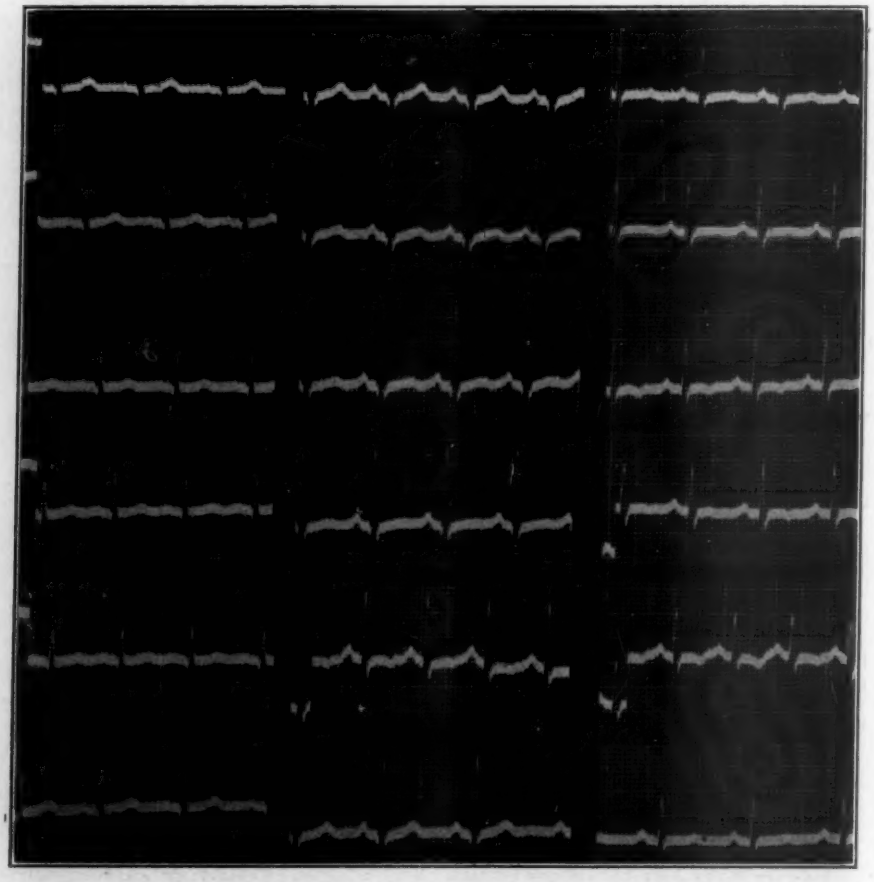

Fig. 3.—E. B. Age, 20. Normal heart. Played football and baseball until 2 years before. Test: 12½ minutes. Discontinued because of marked cyanosis. First record, standard 3 leads. Second, third, fourth, and fifth records, 4, 7, 10½, and 12 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

3. (30 to 40 years.) One record of a 31-year-old man with very good exercise tolerance showed complete eradication of T_2. In four records considerable change in the height of the T wave was seen; in three only moderate diminution was noted; and in two there was almost none.

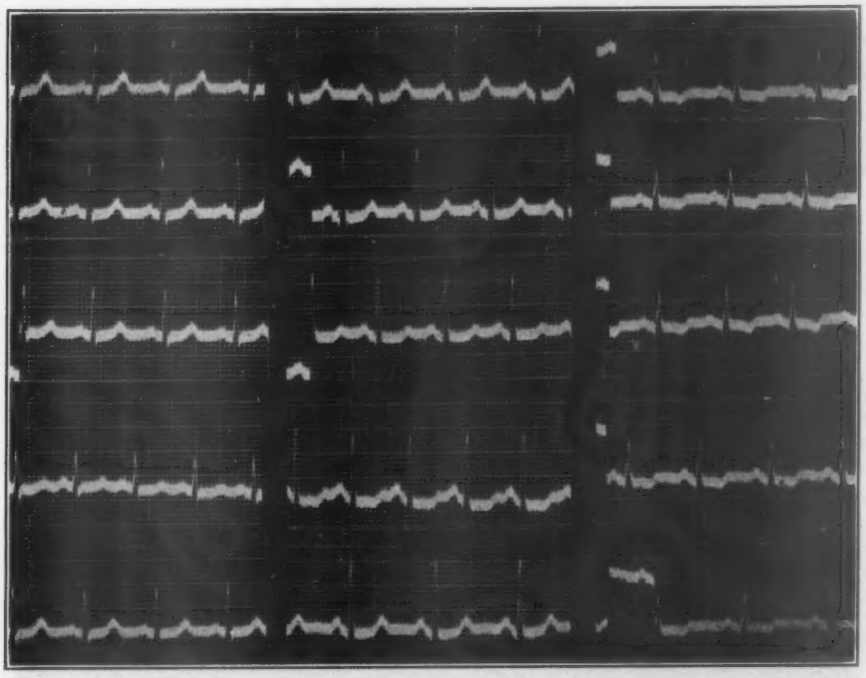

Fig. 4.—A. K. Age, 24. Normal heart. Used to be good long distance swimmer. Test: 8 min. Discontinued because of dyspnea and dizziness. First record, standard 3 leads, second, third, and fourth records 3½, 5½, and 8 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

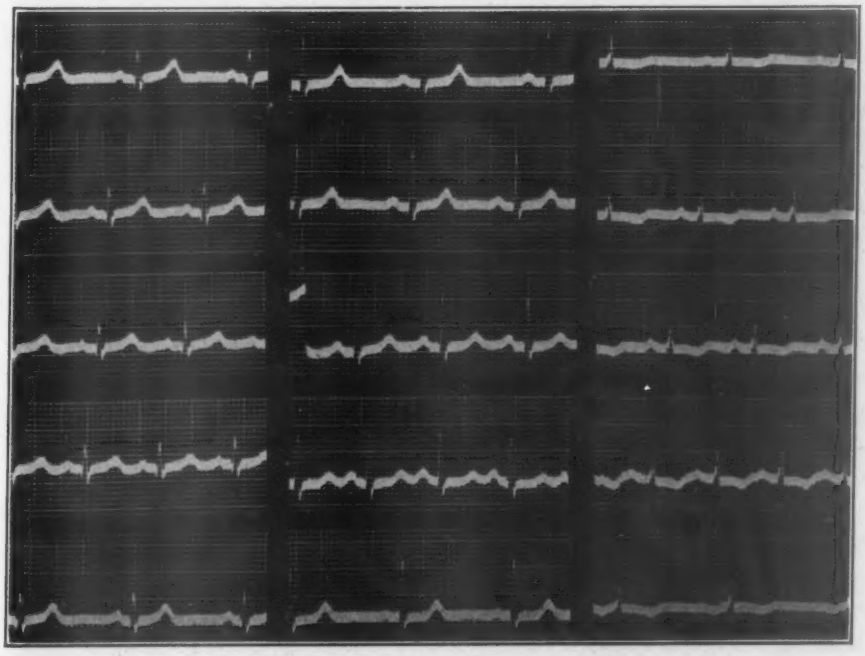

Fig. 5.—J. M. Age, 25. Normal heart. Test: 11 min. Discontinued because of feeling of weakness and shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 3, 6, and 10 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

An example of the average diminution of the T wave in Lead II in this group is seen in Fig. 6, in which T decreases to approximately half its original height. Correlation between T-wave diminution and exercise tolerance was very distinct. One of the subjects, in whose records no change occurred, was of the asthenic type, and the other was a young woman who has suffered from purulent otitis media since childhood.

4. (40 to 50 years.) Changes in the T wave became abruptly less pronounced in this group. Decrease of T_2 to less than half its original height was not encountered, and in three records there was no change at all. The average record showed a diminution of about one-fourth of the original height of the T wave (Fig. 7).

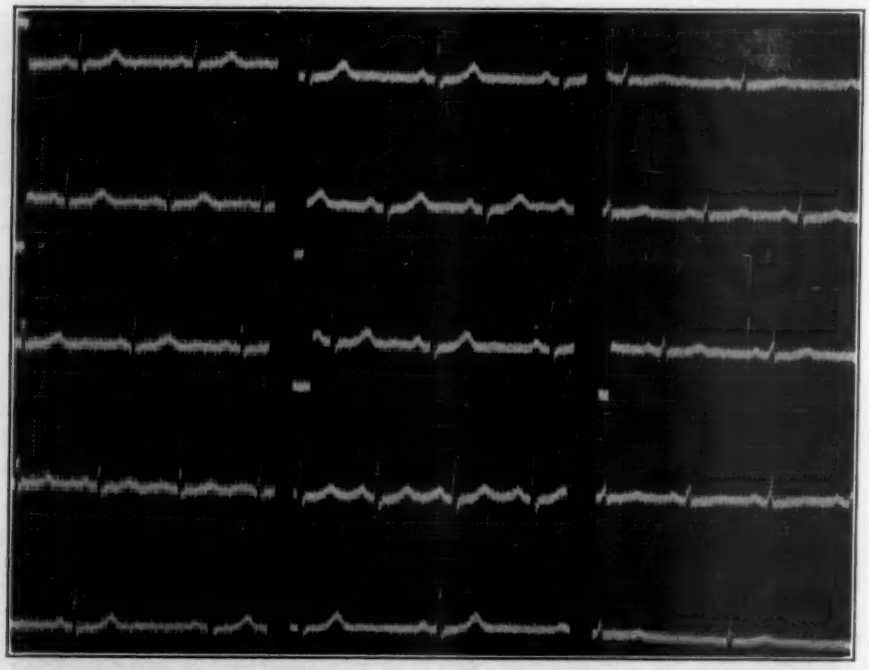

Fig. 6.—E. J. Age, 35. Governess. Normal heart. Test: 14½ min. Discontinued because of dyspnea and cyanosis. First record, standard 3 leads. Second, third, and fourth records, 3½, 7½, and 14 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

5. (50 to 70 years.) A further waning of change was noted in the older age group. Only two records showed a diminution of as much as one-third the original height of the T wave. One of these records was obtained from a man who has had long military training, has lived in the tropics for ten years, and appears and acts like a much younger man (Fig. 8). The other man is an assiduous golfer. Five records showed very slight diminution, and three none at all.

Table I summarizes the specific results of the tests in the age groups studied. Emphasis has been put upon changes in Lead II because they were more readily visible and measurable. Corresponding changes,

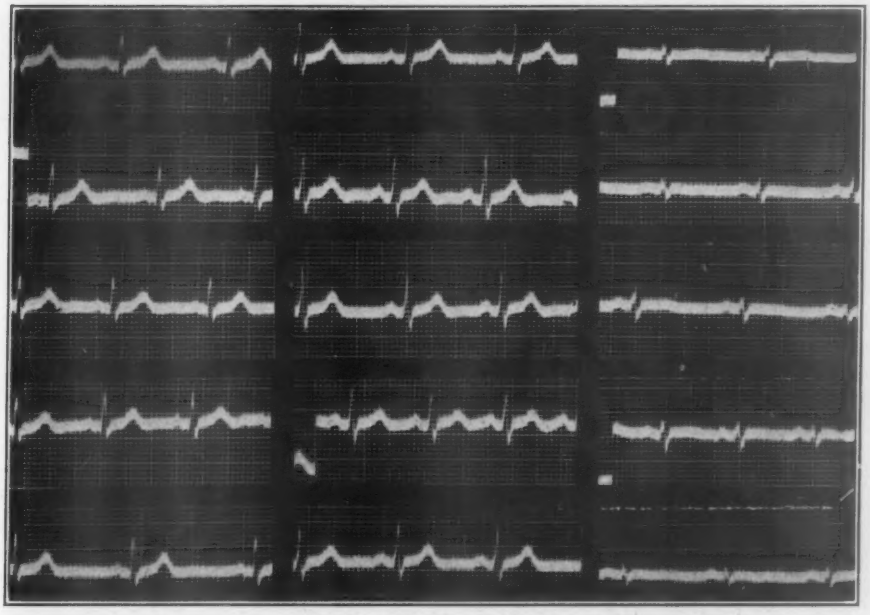

Fig. 7.—E. L. Age, 44. Normal heart. Test: 13 min. Discontinued because of shortness of breath and slight dizziness. First record, standard 3 leads. Second, third, and fourth records, after 4, 7, and 12 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

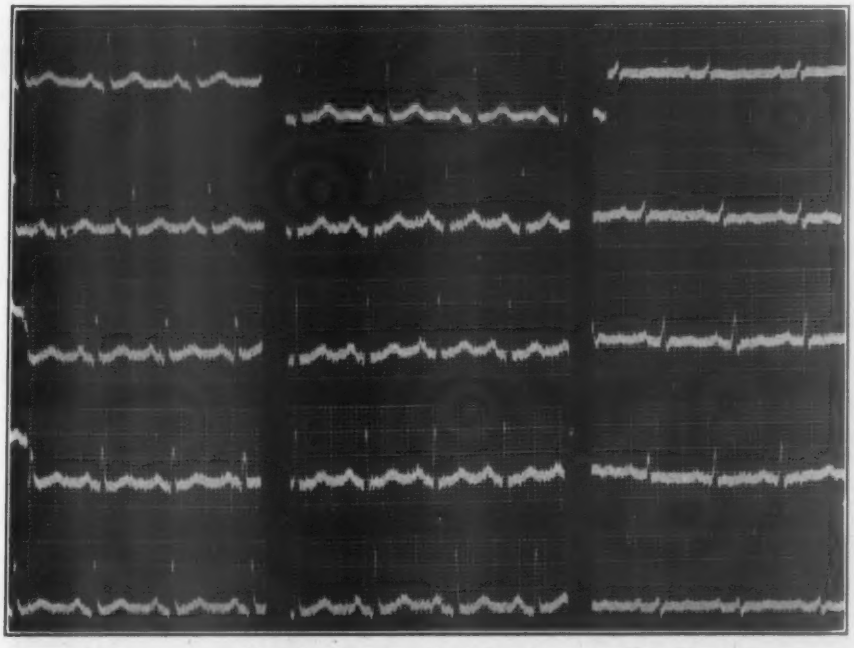

Fig. 8.—M. R. Age, 63. Normal heart. Test: 12 min. Discontinued because of heat in the head and flushes. First record, standard 3 leads. Second, third and fourth records, 4, 7½, and 11 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

TABLE I

NAME	AGE	EXERCISE	LENGTH OF TEST (MIN.)	PULSE RATE BEFORE	PULSE RATE END	PULSE RATE AFTER	T WAVE BEFORE	T WAVE END	T WAVE AFTER	S–T BEFORE	S–T END	S–T AFTER	DIMINUTION OF T_2 IN %
Age Group 15–20													
M. B.	16	much	10	62	94	57	2	0	2	0	0	0	100
H. W.	17	average	11	54	115	63	4	½	3½	0	0	0	87 ½
M. S.	17	little	12½	81	96	83	2½	½	2	−¼	−1	0	80
F. S.	18	average	10½	61	107	61	4	1¼	3¾	½	0	¾	68 ¾
D. S.	18	little	5½	83	107	85	2¼	1½	2	0	0	0	33 ⅓
F. T.	18	very	7	69	90	79	1½	0	1¾	−½	−1	−½	100
J. W.	18	very	10	75	143	79	3	0	1¾	−⅛	−1	−¼	100
W. B.	19	much	10½	69	103	96	3	1½	3	0	0	0	50
E. B.	20	very	12½	100	125	85	1½	0	1½	0	0	0	100
H. B.	20	little	10½	90	103	79	3	2	3	0	0	0	33 ⅓
Age Group 20–30													
A. H.	23	average	14½	62	90	60	5½	3	5	0	0	0	46
L. F.	23	much	10½	90	125	79	3	½	3	0	0	0	83 ⅓
M. H.	24	little	10	79	107	63	2	1¼	2	0	0	0	37 ½
N. R.	24	much	8½	90	120	79	1½	¼	1¾	−½	−½	−½	90
A. K.	24	much	8	94	125	85	2	0	1¾	−¼	−1½	−½	100
A. L.	25	little	8	111	120	94	2½	1½	3½	0	−½	0	40
J. M.	25	much	11	61	111	63	2½	1	2¼	0	−¼	0	60
G. A.	26	little	11	85	103	88	3	1½	2¾	0	0	0	50
W. M.	26	average	10	85	120	94	4	2	4	0	0	0	50
C. Z.	28	much	10½	79	103	83	2½	½	2½	0	0	0	80

TABLE I—CONT'D

Age Group 30–40													
M. S.	30	average	10½	77	103	77	1½	1½	1½	0	0	0	0
F. P.	31	much	9	71	150	85	2	0	1	0	−1	0	100
R. R.	32	average	10½	88	107	79	3	1½	3	0	0	0	50
A. R.	33	little	6	65	107	83	2	1¼	2½	0	0	0	37 ½
G. H.	34	much	12	65	94	66	2	¼	1¼	0	−⅛	0	87 ½
F. H.	35	average	15½	79	107	75	2½	1½	2½	0	0	0	40
E. J.	35	average	14½	60	96	55	2	1	2	0	0	0	50
M. H.	36	average	11	73	103	77	2	½	1½	0	−¼	−¼	75
E. K.	37	average	10¼	57	107	62	4	2	3	0	0	0	50
E. W.	37	little	10½	83	103	85	1	1	1	−¼	−¼	−¼	0
Age Group 40–50													
R. B.	41	little	10½	65	94	71	2¾	2	2	0	−⅛	0	27 ⅓
S. M.	41	average	9½	88	107	94	2¼	1½	2	0	0	0	33 ⅓
E. M.	41	little	9½	94	103	90	1½	1¼	1½	0	0	0	16 ⅔
D. S.	41	average	15	68	77	62	4½	4½	4½	0	0	0	0
E. L.	44	average	13	69	100	65	3	2	3	0	0	0	33 ⅓
N. L.	46	none	12	94	100	88	2¼	2¼	2½	0	0	0	0
W. M.	47	average	13	54	69	55	3	2½	3	0	0	0	16 ⅔
M. F.	48	average	11	85	103	79	4	2½	3½	0	0	0	37 ⅓
P. B.	49	average	10	79	94	79	2	1¼	2	0	0	0	37 ⅓
A. P.	49	average	11	79	94	88	1½	1½	1¾	0	0	0	0
Age Group 50–70													
A. F.	52	average	9	90	103	100	3	2½	3	0	0	0	16 ⅔
W. M.	53	average	11½	63	100	75	2½	2	2¼	0	0	0	20
J. P.	55	average	11	75	83	71	2	1½	2	0	0	0	25
F. E.	55	average	11½	79	94	83	1½	1½	1½	−¼	−¼	−¼	0
H. M.	55	little	11½	83	88	73	2½	2	3	0	0	0	20
E. P.	62	little	9	62	83	55	1½	1½	1½	0	0	0	0
M. R.	63	average	12	88	107	96	1½	1	1½	0	0	0	33 ⅓
G. P.	65	none	9½	81	88	75	3	3	3	0	0	0	0
E. H.	65	much	9½	60	81	62	3	2	3	0	0	0	33 ⅓
R. S.	65	little	10½	68	100	69	1	⅞	1	−¼	−1	−1	12 ⅓

however, were found in all leads. The tendency to diminished response to oxygen deficiency, with advancing age, as measured roughly by changes in the height of the T wave, is very obvious (Fig. 9). Furthermore, there appears to be a striking correlation between the amount of bodily activity and decrease in the height of the T wave. Complete eradication of the T wave (100 per cent change) occurred exclusively in persons who were extremely active or in athletes.

TABLE II

AGE IN YEARS	% DECREASE IN HEIGHT OF T WAVE
15 to 20	75.3
20 to 30	63.7
30 to 40	49.0
40 to 50	20.2
50 to 70	16.1

This observation of the varying reaction in different age groups has, as far as the author is aware, not been made before. An indirect deduction can be made by comparing the classical tests made by Greene and Gilbert, and those made by Katz, Hamburger, and Schutz, in both cases on normal subjects. The former performed their experiments on members of the government aviation service, obviously younger people. The six curves published show almost complete eradication of T_2 near the end of the test, whereas in the latter study, which probably dealt with persons of various ages, only four out of sixteen showed a radical change.

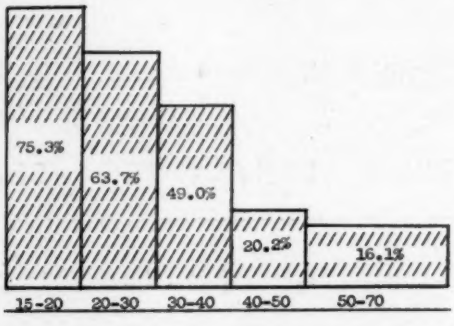

Fig. 9.—The average diminution of the height of T_2, expressed in percentage, in the various age groups.

In summary, the following observations were made in fifty normal subjects.

1. Gradually induced anoxemia produces an acceleration of the heart rate, the degree of which varies individually.

2. Changes in the electrocardiogram coincide with the gradually decreasing oxygen intake, starting soon after the beginning of the experiment.

3. These changes are always of the same general nature; they consist of flattening, eradication, or, at times, inversion of the T wave, and occasionally depression of the S-T segment, and tend to occur in all three leads.

4. The electrocardiogram usually returns to normal within three to five minutes after the induction of anoxemia is stopped.

5. The effect of oxygen deficiency, as measured by diminution in the height of the T wave, lessens considerably with advancing age.

6. There seems to be a striking correlation between exercise tolerance and the degree of diminution in the height of the T wave.

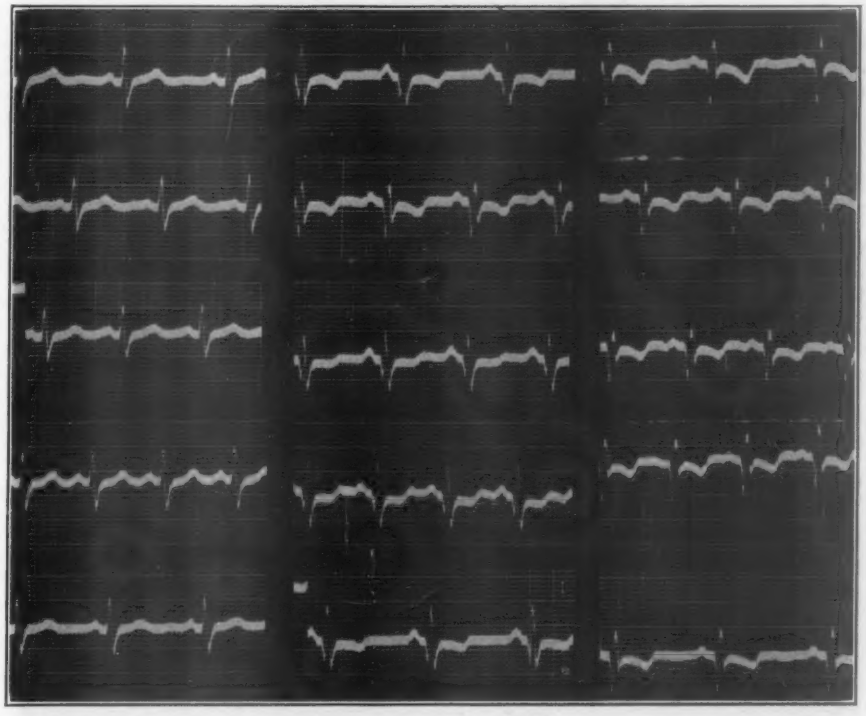

Fig. 10.—M. H. Age, 50. Electrolysist. 2½ years before, first attack of precordial pain, lasting a few minutes. Free of symptoms for 1 year. Never stopped working. Walks 10 blocks and more. Test: 8½ min. Discontinued because of heat in the head and dyspnea. First record, standard 3 leads. Second, third, and fourth records, 3, 5, and 8 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

OBSERVATIONS ON PATIENTS WITH HEART DISEASE

The changes in the electrocardiogram following anoxemia induced in patients with heart disease are still under study, but a few observations might be included here. Of seven patients suffering from angina pectoris, none developed anginal pain at any time during the experiment. Of twenty experiments on patients with various types of heart disease, less than half have shown changes during periods of anoxemia, and only half of these are changes of major degree. The disease in the cases last mentioned was symptomatically mild. Several minutes after the

test was stopped, the electrocardiogram had often not returned to the previous state. Some changes noted in patients with heart disease had characteristics which seemed somewhat different from those seen in normal subjects. Whereas in normal subjects the changes followed the same tendencies in all three leads, in patients with heart disease they were at times more manifest in one lead than in the others in the successive records of an experiment (Fig. 10). From the literature,

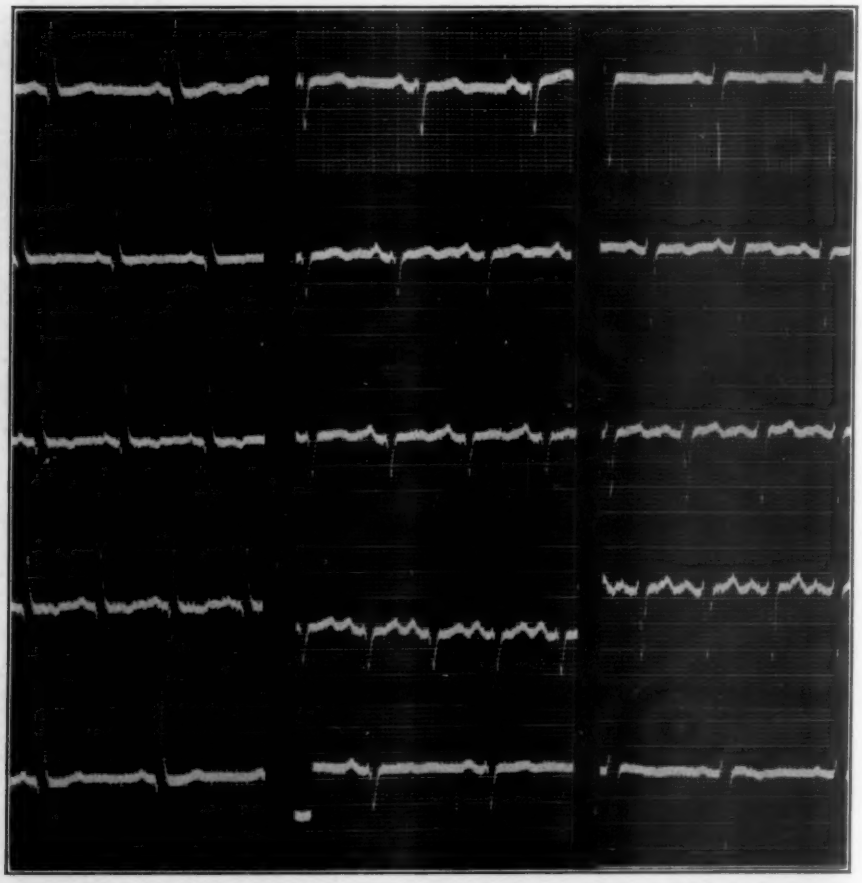

Fig. 11.—H. B. Age, 65. Formerly a salesman. Walks an average of 5 miles a day without discomfort. Blood pressure: 140/78. Test: 10½ min. Discontinued because of shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 3, 7, and 10 minutes after beginning to rebreathe. Last record after 3 min. of breathing room air.

as well as from my own observations, the impression obtained was that in experiments on persons whose intraventricular conduction time was delayed originally the changes during the experiment were of a relatively high degree but the deviation from the characteristics observed in the records of normal subjects was more marked.

One case, that of a 65-year-old man who had never complained of his heart, deserves comment (Fig. 11). The standard record showed a

slurred QRS complex, the duration of which was 0.11 second, exaggeration of the amplitude, and marked left axis deviation, and the T waves in Leads I and III were in the same direction as the QRS complexes. Surprisingly enough, during the course of the experiment the T waves altered their directions so that they came to lie opposite to the main deflection. (The shifting of the axis during the test occurred in all groups studied, but not in combination with the reversal of the direction of the T waves, as in this case.) This interesting observation suggests a possibility for the diagnosis of some types of intraventricular block in its early stages.

DISCUSSION AND COMMENT

The induction of gradually increasing anoxemia in all of the experiments performed, whether on normal subjects or patients with heart disease, was not accompanied or followed by any untoward effect. The symptoms of moderate discomfort which appeared near the end of the period of rebreathing disappeared instantly after the test was stopped. The complaints were mostly of shortness of breath, sensation of heat, and dizziness. Occasionally some aching in the arms and legs was described; some individuals complained of headache. None fainted or became unconscious. The fact that not one of seven patients with angina pectoris developed chest pain, a result which is different from that of other investigators, might be attributed to earlier discontinuation of anoxemia. Moderate discomfort was the signal for discontinuation. In one instance the experiment was stopped by the operator because cyanosis became more marked. This subject did not complain of any discomfort in spite of complete eradication of his T wave. It would appear, then, that with proper care there is no risk for the patient.

It may be added that experiments with vigorous breathing and exercise did not reproduce the changes observed during a period of anoxemia. Analysis of the successive records made during rebreathing, including records before and after, seems to provide new and promising possibilities for obtaining some idea concerning the intrinsic strength of the heart. I suggest that we call such a sequence of records the "anoxygram," for purposes of abbreviation.

Two interesting facts emerge. The degree of change in the T wave decreases strikingly as age advances. It is also obvious that in athletic individuals the changes appear to be greater.

These observations seem to be contrary to the general notion of the significance of the T wave, since flattening of T waves is usually regarded as evidence of myocardial impairment. The fact that the highest degree of reduction in the height of the T wave during anoxemia occurs in young, athletic subjects suggests strongly that these great changes are associated with greater adaptability. Conversely, the lack or absence of change in older and enfeebled persons can be taken as indicative of their inability to compensate for lowered oxygen tension.

Of course, it might also be argued that the hearts of older persons, because of their frequent exposure to anoxemia, fail to react to the stimulus of decrease in oxygen tension. It becomes clear, from this discussion, that the precise mechanism which leads to the changes in the T wave is imperfectly understood. Regardless of theoretical considerations, however, the practical evaluation of changes in the T wave during anoxemia and the effect of age and physical endurance on these changes are clear.

The result of the experiments on persons with normal hearts provides evidence that the degree of T wave changes during periods of induced anoxemia may be useful as an appropriate measure of the functional capacity of the cardiac muscle.

SUMMARY

1. The effect on the electrocardiogram of anoxemia induced by rebreathing was studied.

2. It was found that in persons with normal hearts anoxemia produced uniformly and progressively in all three leads a flattening of the T wave and occasionally a depression of the S-T segment.

3. The degree of the T wave flattening was found to be very high in young subjects. It diminished greatly with advancing age. In the subjects between fifteen and twenty years of age, the average percentage of the diminution of T_2 was 75.3 per cent; in those between twenty and thirty, 63.7 per cent; between thirty and forty, 49 per cent; between forty and fifty, 20.2 per cent; and between fifty and seventy years of age, 16.1 per cent.

4. There was also a striking correlation between the amount of bodily activity and the degree of electrocardiographic change. Complete eradication of the T wave was seen only in very active or athletic young people.

5. The results of these observations were discussed from theoretical and practical points of view. Electrocardiograms made before, during, and after rebreathing would appear to be valuable in testing the functional capacity of the cardiac muscle.

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57 WEST 58TH STREET

THE SIGNIFICANCE OF RHEUMATIC ACTIVITY IN CHRONIC RHEUMATIC HEART DISEASE*

Part II. A Method of Classification

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ONE of the factors causing cardiac dysfunction in adults with rheumatic cardiac disease is the persistence of prolonged and progressive active infection, sometimes so mild as scarcely to be detectable, especially during symptomless periods.[1] Insufficient use of more specific means for ascertaining the degree of rheumatic activity has resulted in inadequate knowledge concerning the course of the disease, particularly in the chronic form encountered in rheumatic cardiac affection.

Since the degree of rheumatic activity varies, even when of low grade, from discontinuous to continuous,[1] a classification was adopted for the purpose of ascertaining the degree. Leucocytosis was chosen as the criterion because it occurs both when the cardiac rhythm is normal and in the presence of auricular fibrillation, and because of the simplicity of the technique of counting leucocytes and a knowledge of the normal range of the leucocyte count.[1, 2]

Although the amount of leucocytosis is indicative of the severity of the infection in acute polyarthritis,[8, 9] the continued presence of any leucocytosis is more significant of the chronic form.[1]

METHCD OF CLASSIFICATION

In patients in whom the deviations from a normal leucocyte count (below 9,000 cells) were 10 per cent, or less, the disease was considered as being inactive; the remainder were divided into three groups, depending on the amount of the deviation. In any case the degree

Table I

Classification of Rheumatic Activity

	Percentage of total number of leucocyte counts above 9,000
Inactive	0- 10 per cent
First degree activity	11- 40 per cent
Second degree activity	41- 70 per cent
Third degree activity	71-100 per cent

Received for publication Nov. 7, 1938.

*This is the third article on investigations undertaken at the New York Cardiac Shop, conducted under the auspices of the Committee on Cardiac Clinics of the New York Heart Association. This study was made possible by grants from the Hofheimer Foundation for three years, the New York Foundation for two years, and the Altman Foundation for one year. The remainder of the fund was subscribed by the Board of Directors of the New York Cardiac Shop. This Board was created by the Board of Directors of Irvington House.

of abnormality depended on the percentage of abnormal to the total number of counts (Table I). For example, a patient exhibiting abnormal leucocyte counts to the extent of 50 per cent of his total number of counts would be classified as second degree, 80 per cent as third

TABLE II

RANGE OF THE LEUCOCYTE COUNTS AND AVERAGE LEUCOCYTE COUNTS IN EACH CASE

CASE NO.	AGE	FUNCTIONAL CLASS.	RHYTHM	LOWEST	HIGHEST	AVERAGE
Inactivity						
3. E. B.	17	IIA	RSR*	4,300	11,900	7,200
8. C. B.	30	IIB	AF†	4,600	11,300	6,900
16. B. G.	16	IIA	RSR	4,400	11,300	6,900
18. F. G.	17	IIB	RSR	4,100	10,600	7,000
22. W. H.	40	IIA	RSR	5,200	8,800	7,200
28. I. L.	21	IIB	RSR	4,100	6,900	5,400
38. E. P.	17	IIB	RSR	4,500	8,300	6,400
41. J. P.	24	IIB	RSR	5,200	6,000	5,600
53. M. So.	24	IIB	AF	6,000	9,000	7,800
Group Average		22.9 years		4,700	9,300	6,700
First Degree Activity						
2. T. A.	15	IIB	RSR	4,300	12,200	8,600
4. B. Ba.	17	IIA	AF	7,500	12,400	9,400
5. B. Bn.	15	IIA	RSR	5,100	12,400	8,500
9. S. B.	30	IIB	RSR	3,200	10,600	7,800
11. E. C.	17	IIB	RSR	4,400	12,000	7,800
24. C. H.	18	IIB	AF	5,100	10,800	7,800
31. B. M.	19	IIB	RSR	4,800	13,600	7,800
33. M. My.	21	IIB	RSR	4,500	15,000	8,000
43. S. R.	23	IIB	RSR	6,500	12,400	8,700
44. R. R.	36	IIB	AF	5,200	12,000	7,900
49. Ia. S.	28	IIB	AF	4,200	11,800	7,800
52. H. S.	16	IIB	RSR	4,500	15,600	8,300
55. G. S.	23	IIA	RSR	4,000	16,500	7,500
56. I. Sh.	27	IIA	RSR	3,000	14,500	8,000
57. M. Sk.	44	IIB	AF	3,800	15,700	7,300
58. Hl. S.	17	IIA	AF	3,600	14,800	7,800
Group Average		22.9 years		4,600	13,000	8,100
Second Degree Activity						
7. S. B.	17	IIB	RSR	5,000	17,000	10,100
10. M. C.	22	IIA	RSR	7,900	11,700	9,600
12. J. D.	18	IIA	AF	5,600	14,700	10,100
13. L. D.	17	I	RSR	6,300	11,800	9,400
15. N. F.	21	IIB	RSR	4,700	17,200	9,600
19. D. G.	18	IIB	RSR	5,600	14,600	9,400
23. F. Hs.	17	IIB	RSR	4,100	17,500	9,100
25. S. Ky.	16	IIB	RSR	4,600	17,100	10,100
32. E. My.	22	IIB	RSR	6,600	16,700	10,000
37. A. O.	16	IIA	RSR	7,000	10,900	9,300
39. C. P.	18	IIB	AF	5,000	15,400	9,200
46. R. S.	17	IIB	RSR	4,700	14,000	8,900
50. J. S.	26	IIB	RSR	5,700	15,400	10,000
51. Ie. S.	20	IIB	AF	4,800	14,400	9,400
54. D. S.	17	IIB	RSR	4,100	12,100	7,600
Group Average		19 years		5,400	14,700	9,500

*Regular sinus rhythm.
†Auricular fibrillation.

TABLE II—CONT'D

CASE NO.	AGE	FUNCTIONAL CLASS.	RHYTHM	LOWEST	HIGHEST	AVERAGE
Third Degree Activity						
1. P. A.	16	IIB	RSR	7,900	19,900	13,100
6. H. B.	19	IIB	RSR	5,100	18,100	10,600
14. J. E.	31	IIB	RSR	9,200	12,200	11,300
17. H. G.	17	IIA	RSR	10,000	13,200	11,700
20. A. G.	25	IIB	AF	10,000	15,200	12,300
21. F. Hr.	20	IIB	RSR	9,100	10,300	9,900
26. R. K.	30	IIB	AF	5,800	12,400	9,500
27. S. Km.	24	IIA	RSR	7,700	17,000	12,600
29. R. L.	20	IIB	RSR	5,600	18,000	10,700
30. E. L.	17	IIA	RSR	4,900	22,100	11,500
34. E. Mz.	25	IIB	RSR	10,200	16,200	14,200
35. M. Ma.	17	IIB	RSR	9,000	14,700	11,300
36. J. O.	16	IIB	AF	6,200	19,900	11,500
40. M. P.	19	IIB	RSR	6,900	13,000	10,200
42. P. P.	17	IIB	RSR	6,000	17,000	10,200
45. A. R.	28	IIB	AF	11,800	16,200	13,700
47. M. Sr.	17	IIB	RSR	9,100	13,900	11,800
48. E. S.	17	IIB	RSR	7,100	13,700	10,200
59. E. Z.	18	IIB	RSR	7,100	18,500	11,400
Group Average		20 years		7,900	16,100	11,500

degree, and so on. By this means, the disease was classed as inactive in 9 cases, and as active in the first degree in 16, in the second degree in 15, and in the third degree in 19.

The range and the average of the leucocyte counts in each case exhibited progressive increases from the stage of inactivity to the third degree (Table II, Fig. 1). On the average, patients exhibiting inactivity and activity of the first degree were somewhat older (3 to 4 years) than those with activity of the second and third degree.

In order to test the value of this method of classification, it was checked with other criteria of rheumatic activity. For this purpose the temperature and pulse rate (in patients with normal rhythm) were selected and the percentage that were abnormal was estimated

TABLE III

COMPARISON OF OTHER CRITERIA OF RHEUMATIC ACTIVITY WITH THE VARIOUS DEGREES OF ACTIVITY OBTAINED BY THE CLASSIFICATION

	ABNORMAL LEUCOCYTE COUNTS	ABNORMAL TEMPERATURE	ABNORMAL PULSE RATES (RSR*)	TRANSIENT ABNORMALITIES IN ELECTROCARDIOGRAMS	ADDITIONAL NEW VALVE LESIONS	ACUTE CARDITIS	CARDIAC DEATHS
Inactivity	5.4%	6.6%	29.5%	14.0%	22.0%	22.0%	22.0%
First degree activity	24.4%	7.7%	26.2%	60.0%	0.0%	25.0%	41.0%
Second degree activity	56.6%	9.5%	40.6%	67.0%	26.4%	13.3%	33.0%
Third degree activity	81.0%	15.4%	53.5%	77.0%	31.6%	42.1%	53.0%

*Regular sinus rhythm.

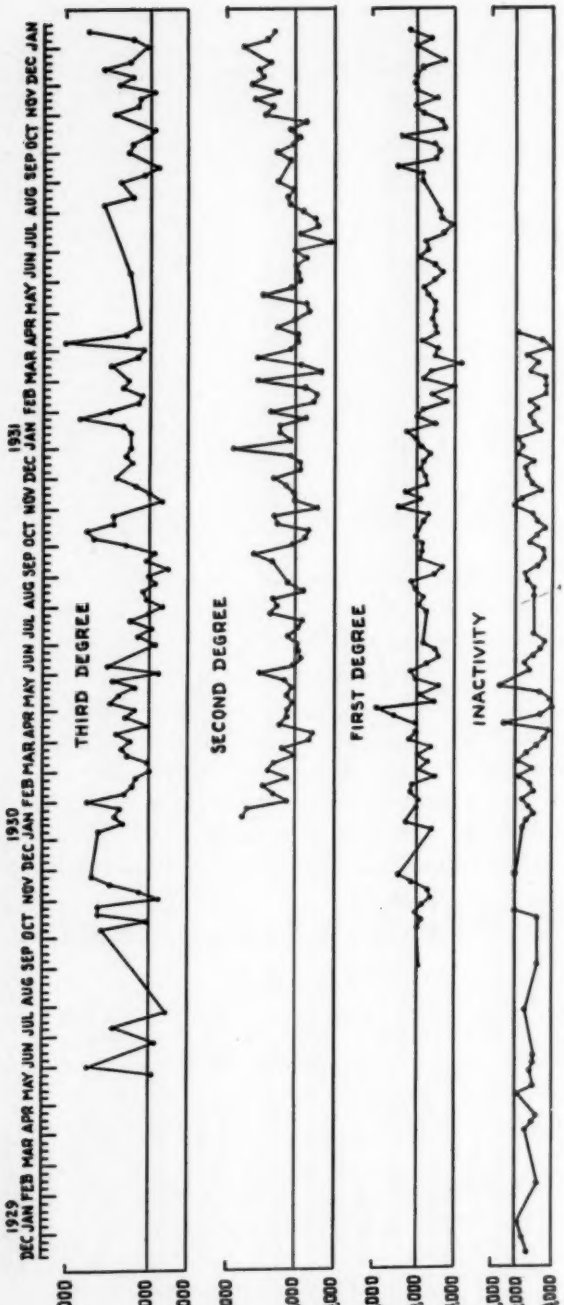

Fig. 1.—Leucocyte curves of representative cases in each degree of activity.

(Table III). Transient changes in the electrocardiograms, the development of new valvular lesions, the presence of acute carditis, and the percentage of deaths attributed to cardiac disease were also studied (Table III). The result suggests an increase in the severity of rheumatic activity parallel with the leucocyte count index.

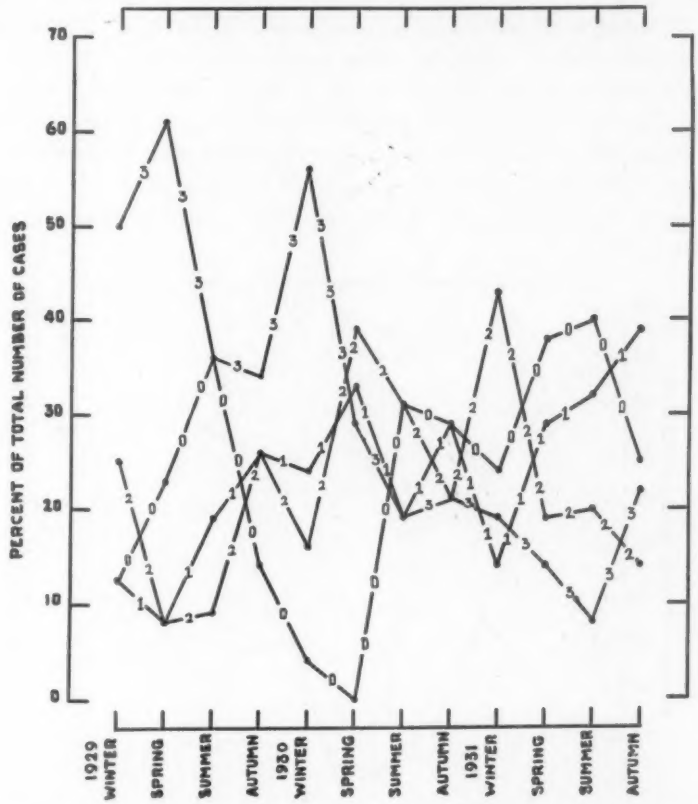

Fig. 2.—Seasonal variations of the degrees of activity. The numerals 0, 1, 2, 3, which interrupt the curves, serve to identify the classes and to make possible tracing the course of the curves.

APPLICATION OF CLASSIFICATION

Whether or not a change in the degree of severity took place with changes in the season of the year has been studied. In Cases 3 and 8, in which the disease had been classified as inactive (Table IV), activity first appeared during the summer of 1931 (Case 3) and the spring of 1930 (Case 8). In most cases of first degree activity cyclic periods of activity and quiescence occurred, whereas quiescence was only occasional in the second and third degree groups. It was interesting to observe the gradual shift of the degree of activity from season to season, increasing or decreasing by single stages, rarely abruptly by more. This phenomenon is important because it depicts the fact that rheu-

matic activity may develop or recede slowly in the absence of signs and symptoms. During the winter of 1932 four patients (Case 53, first degree; Cases 25 and 51, second degree; Case 36, third degree, Table IV) manifested activity of the third degree as exhibited by their leucocyte counts, but had a normal cardiac reserve (Functional Classification I). All of the patients with obvious evidence of acute carditis showed evidence of pre-existing rheumatic activity.[1] Although cardiac damage (acute carditis) was more apparent in patients with leucocyte counts of the third degree, it was equally serious but more insidious in its development in those with counts of lesser degrees. Viewed seasonally, diminished cardiac function was found sometimes to occur, therefore, with decreasing rheumatic activity. This was particularly noticeable in patients with long-continued auricular fibrillation.

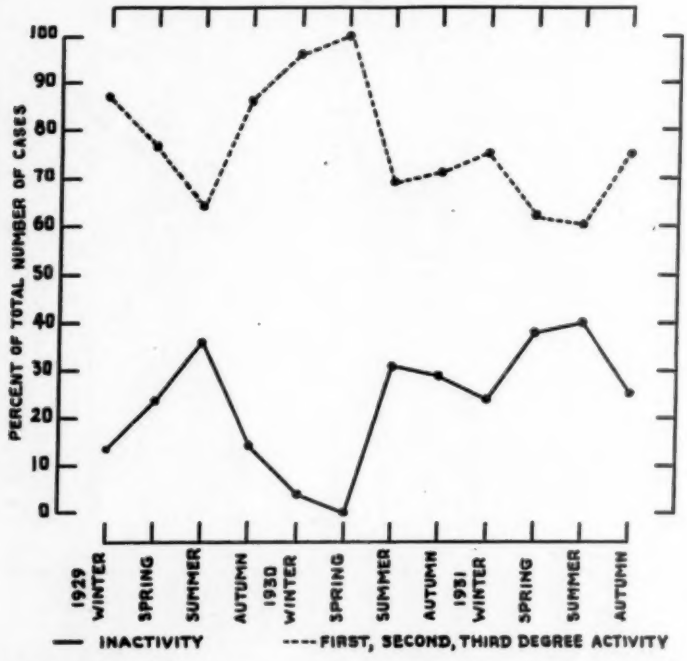

Fig. 3.—Seasonal variation of rheumatic activity based on abnormal leucocyte count percentages; first, second, and third degrees combined and compared with inactivity.

SEASONAL VARIATION OF DEGREE OF RHEUMATIC ACTIVITY

The least activity, according to this classification (leucocytosis), occurred during the summer, but the peak did not always occur in the same season. In 1929 it was in the winter, in 1930 in the spring, and in 1931 in the winter (Figs. 2 and 3). These findings are in accord with those of other observers, though this study was based on leucocyte counts and theirs on clinical manifestations.[3, 4, 5, 6, 7]

TABLE IV

SEASONAL RELATIONSHIP OF DEGREE OF ACTIVITY AND FUNCTIONAL CLASSIFICATION

CASE	1929				1930				1931				1932
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER
						Inactivity							
3. E. B. RSR*											1 IIB-IIA	0 IIA	0 IIA-I
8. C. B. AF†	0‡ IIB-III§	0 III-IIB	0 IIB	0 IIB-III	0 IIB	1 IIB-III	0 IIB	0 IIB	0 IIB	0 IIB			
16. B. G. RSR							0 IIB	0 IIB-III	0 IIB				
18. F. G. RSR										0 IIB	0 IIB	0 IIB-IIA	0 IIA
22. W. H. RSR		0 IIA	0 IIA	0 IIA									
28. I. L. RSR											0 IIB-IIA	0 IIA	
38. E. P. RSR											0 IIB	0 IIB-IIA	0 IIA-I
41. J. P. RSR										0 IIB			
52. M. S. AF											0 IIB-III	0 IIB	

*Regular sinus rhythm.
†Auricular fibrillation.
‡The upper, Arabic, numerals designate the degree of activity.
§The lower, Roman, numerals designate the functional classification and fluctuations when showing more than one figure.

TABLE IV—CONT'D

CASE	1929				1930				1931				1932
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER
First Degree Activity													
2. T. A. RSR											2 IIB	1 IIB-IIA	
4. B. Ba. AF											1 IIA-IIB		
5. B. Bn. RSR											1 IIA-I	1 I	
9. S. B. RSR												1 IIB	
11. E. C. RSR										1 IIB	1 IIB-IIA	1 IIA	0 IIA
24. C. H. AF											1 IIB	1 IIB-III	
31. B. M. RSR									2 IIB-IIA	1 IIB	0 IIB	0 IIB	
33. M. M. RSR				2 IIB	2 IIB	1 IIB-IIA	1 IIA-IIB	0 IIA	0 IIA-IIB	1 IIA	1 IIA	1 IIA	2 I
43. S. R. RSR								1 IIB					
44. R. R. AF			0 IIB-IIA	1 IIB-IIA	1 IIB-IIA	1 IIA	2 IIA-IIB						
49. I. S. AF		0 IIB-III	1 IIB-IIA	1 IIB	1 IIB	1 IIB	0 IIB	1 IIB-IIA	1 IIA-IIB	0 IIB-IIA	0 IIB	1 IIB	1 IIB
53. H. S. RSR											0 IIB-IIA	1 IIA-I	3 I
55. G. S. RSR		2 IIA-IIB	0 IIB-IIA	1 IIB-IIA	2 IIB-IIA	1 IIA	0 IIA	0 IIA	0 IIA-IIB	0 IIB-IIA	0 IIA	0 IIA	0 IIA
56. I. Sh. RSR				1 IIA-IIB	1 IIB	2 IIA	1 IIA	1 IIB-IIA	0 IIA	0 IIA-IIB	0 IIA-IIB	1 IIA	1 IIA
57. M. S. AF						1 IIB	0 III-IIB	0 IIB-IIA	1 IIB	1 IIB			
58. H. S. AF		1 IIA-IIB		0 IIA	1 IIA-IIB	1 IIB-IIA	0 IIB-IIA	0 IIA-IIB					

See legend, Table IV, first section.

TABLE IV—CONT'D

CASE	1929				1930				1931				1932
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER
Second Degree Activity													
7. S. B. RSR	3 IIB-IIA	3 IIB	1 IIB	2 IIB	3 IIB-IIA	2 IIA-IIB	2 I-IIA	1 IIA-I					
10. M. C. RSR											2 IIA		
12. J. D. AF			3 IIA	3 IIA-IIB	3 IIA-IIB	3 IIA	2 IIA	3 IIA	2 IIA	1 IIA-IIB	2 IIB-IIA		3 IIA
13. L. D. RSR												2 I	2 I-IIB
15. N. F. RSR	3 IIB	3 IIB		1 IIB	3 IIB	2 III-IIB	1 IIB	1 IIB-IIA	2 IIB-IIA	2 IIB			
19. D. G. RSR												2 IIB-II	1 IIA-I
23. F. H. RSR					3 IIB-IIA	3 IIB-IIA	3 IIA-IIB	2 IIA-I	2 IIA-IIB	1 I-IIA	0 IIA	1 IIA-I	2 I
25. S. K. RSR					3 IIB	3 IIB-IIA	2 IIA-IIB	2 IIB-IIA	2 IIB-IIA	2 IIA-IIB	1 IIA-IIB	3 IIA	3 IIA-I
32. E. M. RSR								3 IIB-IIA	2 IIA-IIB				
37. A. O. RSR												2 IIB-IIA	
39. C. P. AF		3 IIA-IIB	3 IIB-IIA	2 IIA-IIB	2 IIB-IIA	2 IIA	2 IIA	0 IIA	2 IIA	0 IIA			
46. R. S. RSR				1 IIB	1 IIB	2 IIB	2 IIB-IIA	1 IIA	2 IIA	2 IIA	1 IIA	3 IIA	2 IIA
50. J. S. RSR				2 IIB-IIA	2 IIA-IIB	2 IIB-III							
51. Ie. S. AF								2 IIB-IIA	2 IIB-IIA	2 IIA-I	2 IIA-I	2 IIA-I	3 I
54. D. S. RSR				2 IIB-IIA	1 IIA-IIB	1 IIB-IIA	0 IIA-IIB	1 IIA-IIB	1 IIA-IIB	0 IIA-IIB		1 IIA-I	0 I

See legend, Table IV, first section.

TABLE IV—CONT'D

CASE	1929				1930				1931				1932
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER
Third Degree Activity													
1. P. A. RSR	3 IIB-III	3 III											
6. H. B. RSR	2 IIB-IIA	3 IIA-IIB	3 IIA	2 IIB-III	3 IIB-III	2 IIB-III	3 IIB-III	3 IIB-III	3 IIB	3 IIB-III	2 IIB		3 IIB
14. J. E. RSR					3 IIB								
17. H. G. RSR		3 IIB-III											
20. A. G. AF		3 IIB											
21. F. Hr. RSR				3 IIB-III									
26. R. K. AF												3 IIB	2 IIB
27. S. K. RSR				3 IIA	3 IIA-IIB	3 IIA							

See legend, Table IV, first section.

29.	R. L. RSR	2 IIB-IIA	3 IIA-IIB	3 IIB-III	3 III-IIB	3 IIB	3 IIB	3 IIB-IIA	2 IIB-IIA	3 IIB				
30.	E. L. RSR								2 IIA-IIB	3 IIB	3 IIB	3 IIB-IIA	3 IIA	3 IIA
34.	E. M. RSR		3 IIB-III											
35.	M. M. RSR												3 IIB	
36.	J. O. AF			2 IIB-III	3 IIB-IIA	3 IIB-IIA	3 IIA-IIB	1 III-IIB	3 IIB-III	3 IIA-IIB	3 IIB-III	3 III-IIB	3 IIB-IIA	3 I
40.	M. P. RSR	1 IIB			3 IIB	3 IIB								
42.	P.P. RSR				3 IIB	3 IIB	2 IIA-IIB							
45.	A. R. AF				3 IIB-III									
47.	M. S. RSR	3 IIB												
48.	E. S. RSR					3 IIB	2 IIB	2 IIB-III	3 IIB-III					
59.	E. Z. RSR				3 IIB-III	3 IIB-III	3 IIA	3 IIA						

SUMMARY

1. A method of separating patients with active rheumatic heart disease into classes of increasing degrees of activity is described. It is based on the percentage of abnormal leucocyte counts in each case. Patients placed in the inactive group comprise those whose counts were within the normal range. In nine cases the disease was classified as inactive, in sixteen as active in the first degree, in fifteen as active in the second degree, and in nineteen as active in the third degree.

2. Beginning with the inactive group and proceeding through the groups of first, second, and third degree activity, there was progressive increase in the range and in the average leucocyte counts.

3. The average age of the patients in the inactive and first degree groups was higher than that in the second and third.

4. Using the criteria tested in this study, it was found that rheumatic activity was more intense in patients in the third degree group and least in those in the inactive group.

5. The activity of the rheumatic process was least during the summer of each year.

6. Fluctuation in the degree of activity, according to the classification, was very gradual, usually one degree at a time. Since most acute manifestations of rheumatic activity occurred in the higher degree groups, a pre-existing active phase of a lower degree was usually present. Evidence is adduced to show that there are symptomless periods in patients with third degree activity.

CONCLUSION

Using the leucocyte count as a basis of classification it has been found useful and instructive to divide cases of rheumatic activity into four groups: inactive, first, second, and third degrees, respectively.

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RIGHT VENTRICULAR HYPERTROPHY AND CONGESTIVE FAILURE IN CHRONIC PULMONARY DISEASE

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RIGHT ventricular failure is an important cause of death in chronic pulmonary disease. Chronic cor pulmonale (chronic pulmonary heart disease) is often considered such a rarity that the diagnosis is overlooked or made with great hesitancy in these cases. Chronic cor pulmonale is caused by hypertension in the pulmonary circulation which results from disease of the lungs or its blood vessels. It is characterized pathologically by hypertrophy of the right ventricle and, when the heart fails, by signs of systemic venous congestion. Congestive failure occurs late in the course of the disease.

We have undertaken to ascertain the incidence of cor pulmonale in the more common chronic pulmonary diseases. Inasmuch as the clinical diagnosis of this condition is often unreliable, we base our conclusions on the study of autopsy material in which the pulmonary and cardiac lesions can be clearly recognized and evaluated.

MATERIAL

We reviewed the protocols of all chronic pulmonary lesions listed in the cross index of the 18,000 autopsies done at the Los Angeles County Hospital during the past nineteen years. Cases in which the pulmonary lesions were described as minimal or localized, obviously incapable of affecting the pulmonary circulation, were excluded from our study.

We found that many patients had more than one pulmonary disease and some had heart disease other than cor pulmonale. To evaluate the effect of each pulmonary disease upon the heart we divided the total number of cases of each pulmonary disease into the following groups: (1) Cases in which the patients had only the one pulmonary disease and had no cardiac lesion other than cor pulmonale, hereafter designated as cases "alone"; (2) cases in which the patients had additional pulmonary lesions but no cardiac disease other than cor pulmonale, designated hereafter as "associated pulmonary" cases; (3) cases in which the patients had only the single pulmonary lesion but had cardiac disease other than cor pulmonale, including those with high blood pressure (150/100 or more), designated in this paper as "cardiac" cases (we

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Read before the Section on Practice of Medicine at the Annual Session of the American Medical Association, San Francisco, Calif., June 15, 1938.

Received for publication Nov. 13, 1938.

have entirely excluded from our study the few cases of mitral disease and congenital heart disease which would primarily cause right ventricular hypertrophy); (4) cases in which the patients had both additional pulmonary lesions and had cardiac disease other than the chronic pulmonary heart disease, designated as "associated pulmonary and cardiac" cases (see Fig. 2).

CRITERIA

Estimation of right or left ventricular hypertrophy is most accurately accomplished by weighing each ventricle separately.[1] Since only cardiac weights and mural thicknesses had been recorded by the autopsy surgeon, we were obliged to use the average thickness of the ventricular wall as the criterion of hypertrophy. Hearts in which the right and left ventricular walls measured less than 4 mm. and not more than 12 mm., respectively, in average thickness were considered normal. A right ventricular wall which averaged 5 mm., or a left ventricular wall which averaged over 15 mm. in thickness, was considered definitely hypertrophied. The term "hypertrophy of both ventricles" was used to designate hearts in which both right and left ventricles were definitely hypertrophied, and also hearts in which the wall of the right ventricle

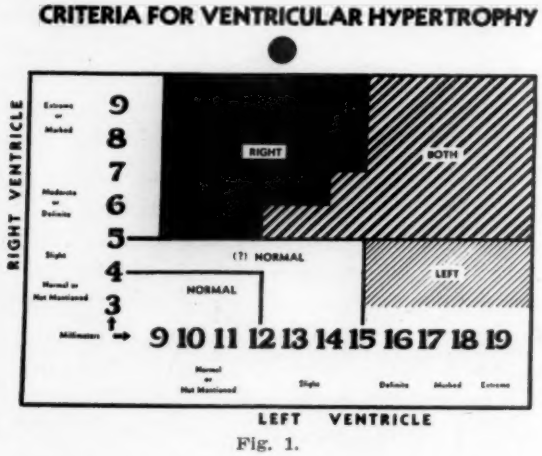

Fig. 1.

was 5 to 6 mm. and the left more than 12 mm. in thickness, or the wall of the right ventricle 6 to 7 mm. and that of the left more than 14 mm. Our criteria, therefore, restrict the term "right ventricular hypertrophy" to those hearts which have a *predominant* right ventricular hypertrophy (Fig. 1, solid black area). Although Thompson and White[2] found that left ventricular strain was the greatest cause of right ventricular hypertrophy, the great majority of their examples of right ventricular hypertrophy would have been listed, by our criteria, under "hypertrophy of both ventricles" (Fig. 1, heavy shaded area). We believe that the percentage of right ventricular hypertrophy in the group of cases "alone" (cases in which the patient had only one pulmonary

disease and no cardiac disease other than cor pulmonale) represents quite conservatively the incidence of cor pulmonale caused by the lesion under discussion.

Our classification still leaves a small group of hearts with questionable hypertrophy of the right or left ventricle which we classed as "questionably normal." In some autopsy records, the thickness of the right ventricle or, rarely, of the left ventricle, was not stated. If not mentioned, we have considered the ventricle as normal. This added an unavoidable error, but one which would minimize and not overemphasize the effect of the chronic pulmonary diseases studied as causes of cor pulmonale. Rarely the ventricles were not measured but described as "slightly," "moderately," or "greatly hypertrophied." Fig. 1 will visualize the criteria used in this study.

The term "definite congestive failure" was reserved for patients who showed marked chronic passive congestion of the liver, associated with either ascites or edema, or with a pathologist's diagnosis of "congestive failure." All cases in which the evidence was less convincing, but suggestive, were classed as "questionable failure."

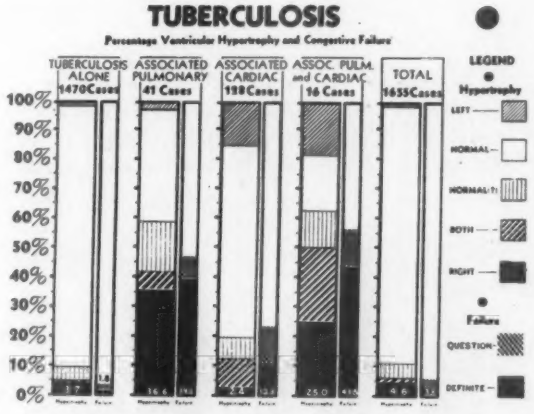

Fig. 2.

RESULTS

Chronic Bronchitis.—In 92 of 185 cases of chronic bronchitis the lungs showed no other pulmonary lesions. In this group we found no case of right ventricular hypertrophy or congestive failure which we felt was caused by the chronic bronchitis. We have, therefore, disregarded the incidental diagnosis of chronic bronchitis in the study of the other pulmonary diseases.

Pulmonary Tuberculosis.—Among the 18,000 autopsies there were 1,655 cases (9.1 per cent) of moderately or far-advanced pulmonary tuberculosis.

In the total of 1,655 cases, approximately 86.8 per cent of the hearts showed no ventricular hypertrophy, while only 4.6 per cent showed

"right ventricular hypertrophy." If, to this 4.6 per cent, are added the cases in which the right ventricle was slightly hypertrophied, but with a mural thickness of less than 5 mm., and the cases in which both ventricles were hypertrophied, the total incidence of right ventricular hypertrophy is still only 10.2 per cent. These figures differ greatly from those recently reported by Nemet and Rosenblatt,[3] who found exclusive hypertrophy of the right ventricle in 33.8 per cent of 71 cases of tuberculosis. Including the cases with hypertrophy of both ventricles, the right ventricle was hypertrophied in 46.5 per cent of their total group.

In 1,470 cases of tuberculosis "alone," we found that 3.7 per cent of the hearts were the seat of pure right ventricular hypertrophy, while 90.8 per cent showed no hypertrophy. We were unable to correlate the cardiac hypertrophy with specific types of tuberculosis, although, of course, it was generally found in advanced cases. In 41 cases with "associated pulmonary" lesions in which pneumoconiosis frequently occurred, the percentage of right ventricular hypertrophy increased to 36.6 per cent, pointing conclusively to the fact that tuberculosis falls far below the average of other chronic pulmonary diseases, especially pneumoconiosis, as a cause of right ventricular hypertrophy (Fig. 2).

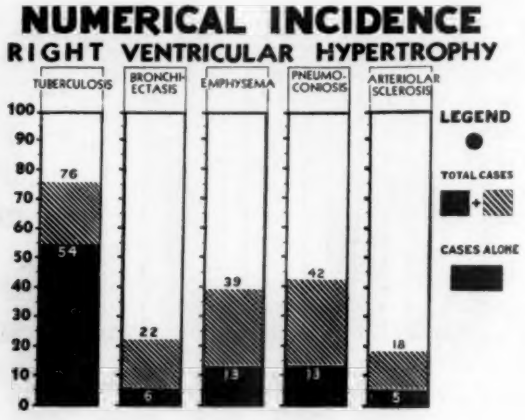

Fig. 3.

The tuberculosis group had the lowest *percentage* of right ventricular hypertrophy of all chronic pulmonary disease groups, except chronic bronchitis. Nevertheless, due to the high incidence of tuberculosis, right ventricular hypertrophy was seen more frequently at autopsy in patients with tuberculosis than with any other pulmonary disease (Fig. 3).

Of the total of 1,655 patients with tuberculosis, there were 3.8 per cent with definite failure and 2.8 per cent with questionable failure, totaling 6.6 per cent. Among the 1,470 patients with pulmonary tuberculosis "alone," 1.8 per cent had definite congestive failure and 1.8 per cent had questionable failure, totaling 3.6 per cent (Fig. 2).

Bronchiectasis.—Bronchiectasis of moderate or marked degree was found in 136 cases. Right ventricular hypertrophy occurred in 16.2 per cent of these patients. In the 68 patients with bronchiectasis "alone," 8.8 per cent showed pure right ventricular hypertrophy, while 82.4 per cent showed no hypertrophy of either ventricle. This was over twice the percentage of right ventricular hypertrophy found in patients with tuberculosis "alone." As in tuberculosis, so in bronchiectasis, association with other pulmonary lesions increased the incidence of right ventricular hypertrophy to over 36 per cent (Fig. 4).

In the entire group of patients with bronchiectasis, 16.2 per cent showed definite congestive failure and 7.4 per cent questionable failure. In the 68 patients with bronchiectasis "alone," there were 4.4 per cent with definite congestive failure and 3 per cent with questionable failure, totaling 7.4 per cent.

Emphysema.—There were 129 cases (0.7 per cent) of moderate or marked emphysema, and 30.2 per cent of these patients presented right ventricular hypertrophy.

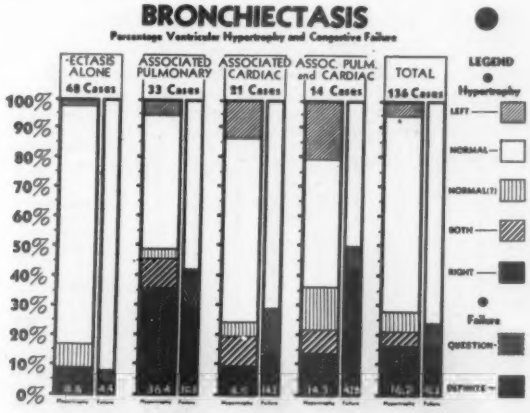

Fig. 4.

Of 45 patients with emphysema "alone," 28.9 per cent had right ventricular hypertrophy, which is nearly the same percentage as in the total group of emphysema cases. If cases in which both ventricles were hypertrophied are also included, the right ventricle was hypertrophied in 47 per cent of the patients in the total emphysema group, as compared with 40 per cent in those with emphysema "alone" (Fig. 5). These figures are in general agreement with the conclusions of Kountz, Alexander, and Prinzmetal,[4] who separated and weighed the right and left ventricles of the hearts of 17 patients with marked emphysema. They concluded that the heart is affected in the majority of cases of emphysema.

In the total group of patients with emphysema, 38.8 per cent showed definite congestive failure, and 20.1 per cent questionable failure, total-

ing 58.9 per cent. Of the 45 patients classed as having emphysema "alone," definite congestive failure occurred in 22.3 per cent and questionable failure in 15.6 per cent, totaling 37.9 per cent.

Asthma.—We did not list the cases of asthma separately. We agree with Lamson,[5] and others, that asthma is a syndrome which may be associated with heart disease, or various pulmonary diseases, or may be due to allergy. Most of the patients with asthma due to allergy, in our series, also had emphysema. In our 45 cases of emphysema "alone," over 50 per cent of the patients were known to have had asthmatic attacks. We also included in this group 6 patients with asthma whose lungs showed slight emphysema. These had approximately the same percentage of cardiac findings as in the rest of the cases of emphysema "alone."

Pneumoconiosis.—In the 18,000 records reviewed, we found 97 cases (0.5 per cent) of pneumoconiosis. We included as pneumoconiosis cases of silicosis, anthracosis with moderate or marked fibrosis, and also fibrosis of unknown etiology, provided the silica content of the wet lung tissue was more than 2.5 mg. per cent.[6*] Fibrosis in anthracosis is generally considered to be due to accompanying silicosis.[7]

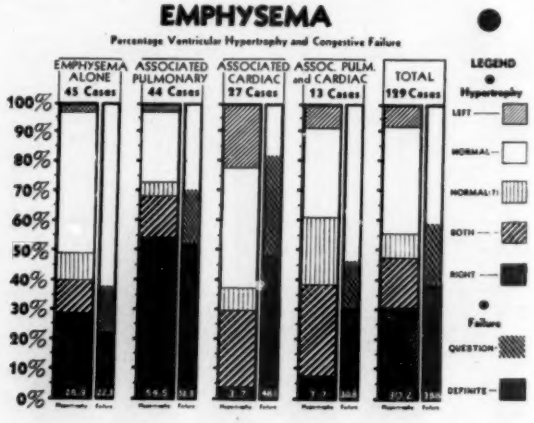

Fig. 5.

In the total group of 97 patients with pneumoconiosis, right ventricular hypertrophy occurred in 43.3 per cent. If instances of hypertrophy of both ventricles are included, the right ventricle was hypertrophied in 58.8 per cent. Of the 24 patients with pneumoconiosis "alone," 54.2 per cent showed right ventricular hypertrophy. If those with hypertrophy of both ventricles are included, 66.7 per cent showed right ventricular hypertrophy. This figure is higher than for the total group of pneumoconiosis. This is due possibly to earlier deaths of patients who had tuberculosis, or cardiac disease other than cor pulmonale (Fig. 6).

*The microdeterminations were kindly done by Albert L. Chaney, Ph.D., chemist at the Los Angeles County Hospital.

Definite congestive failure was present in 51.6 per cent of the total group of 97 patients, and questionable failure in 11.4 per cent, making a total of 63 per cent. Of the 24 patients with pneumoconiosis "alone," 50 per cent showed definite congestive failure and 16.7 per cent questionable failure, totaling 66.7 per cent.

Though Dyson,[8] Jaffe,[9] and others[10, 11] have discussed the cardiac changes in pneumoconiosis, the importance of this complication is not generally appreciated. In our series, contrary to the usual impression, the number of patients who died with congestive failure was even greater than the number of those who had an associated tuberculosis. It has been thought[7] that patients with anthracosilicosis are less susceptible to tuberculosis than patients with pure silicosis. The presence of anthracosilicosis in some of the patients may explain the lower incidence of tuberculosis in our group. Sweany, Porsche, and Douglass[7] state that these cardiac changes occur in advanced cases. In another study,[12] we were able to confirm this opinion. We believe that congestive failure, when due to cor pulmonale, is usually a terminal event.

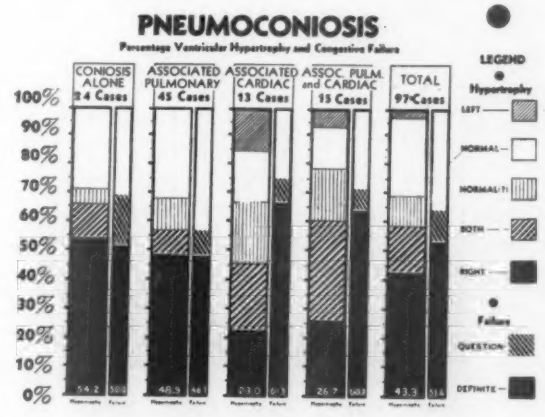

Fig. 6.

Nonspecific Pulmonary Fibrosis.—In 14 cases the fibrosis apparently was not due to tuberculosis or pneumoconiosis. Some were listed as "interstitial pneumonitis, etiology undetermined." Some, from the description in the record, might have been pneumoconiosis, but we were unable to verify this impression. These 14 patients showed approximately the same cardiac findings as did those with pneumoconiosis; 64 per cent had right ventricular hypertrophy, and 42 per cent developed definite congestive failure.

Spinal Deformities.—Only 5 cases of scoliosis or kyphoscoliosis were found in the autopsy index. These were of severe degree, and no doubt many other cases of slight or moderate deformity had gone unindexed. Of these 5 patients, definite hypertrophy of the right ventricle was

found in 3; in one there was dilatation without hypertrophy, and in one no anatomic change. This group is too small to be of statistical value, but the findings agree with those of Bachmann.[13] From a clinical study, Edeiken[14] concluded that spinal deformities, especially scoliosis and kyphoscoliosis, have a profound effect upon the lungs, and that the effect upon the heart is probably secondary to the pulmonary changes in most instances. Our 5 patients all had such pulmonary lesions.

Pulmonary Arteriolar Sclerosis.—The lungs in the group of 26 patients listed as having "pulmonary arteriolar sclerosis" had been carefully sectioned and the arterioles studied because of the marked degree of right ventricular hypertrophy which was found at autopsy. A high incidence of right ventricular hypertrophy and congestive failure in this group was therefore to be expected. Nearly all the hearts showed marked hypertrophy of the right or of both ventricles. Definite congestive failure was present in 61.5 per cent of this entire group and in 57.1 per cent of the 7 patients with pulmonary arteriolar sclerosis "alone."

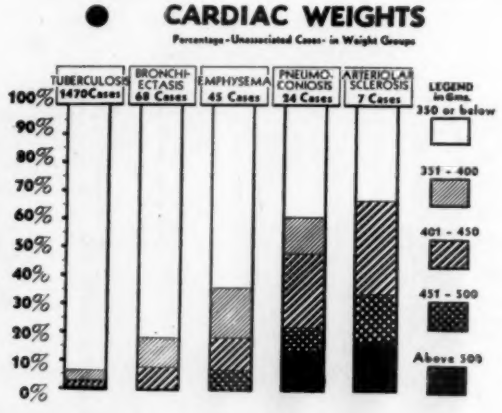

Fig. 7.

Weight of Hearts.—The percentage of hearts with increased weights was found to parallel closely the percentage of thickened right ventricular walls in the various pulmonary disease groups. The tuberculosis group showed the largest percentage of hearts weighing 350 gm. or less. Normal heart weights were next most frequent in bronchiectasis, then came emphysema, while the pneumoconiosis and pulmonary arteriolar sclerosis groups showed the lowest percentage of hearts weighing 350 gm. or less. On the other hand, pneumoconiosis was the only group, with the exception of pulmonary arteriolar sclerosis (a specifically selected group), in which there were hearts weighing over 500 gm. without associated cardiac lesions. Similarly, emphysema and pneumoconiosis were the only groups in which hearts weighing over 450 gm. were found. These facts are shown graphically in Fig. 7.

SUMMARY AND CONCLUSIONS

1. The protocols of all chronic pulmonary lesions indexed in 18,000 consecutive autopsies were studied to ascertain the incidence of cor pulmonale in the more common pulmonary diseases, as evidenced by right ventricular hypertrophy and congestive cardiac failure. These cases were grouped according to their association with other pulmonary or cardiac lesions.

2. Chronic pulmonary disease is an important cause of cor pulmonale. The various pulmonary lesions varied greatly in their effect upon the heart. For comparative analysis, conclusions are drawn only from the group of cases in which there was no other pulmonary or cardiac disease (cases "alone") (Fig. 8).

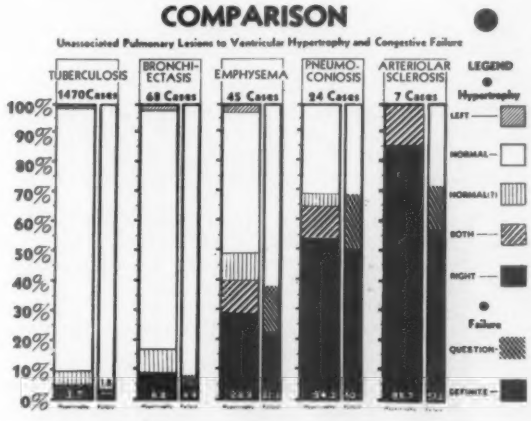

Fig. 8.

3. Pneumoconiosis showed the highest percentage incidence of cor pulmonale. Right ventricular hypertrophy occurred in 54.2 per cent, and definite congestive failure in 50 per cent, of 24 patients without other pulmonary or cardiac disease. The number of patients with pneumoconiosis who died with definite congestive failure was even greater than the number of those who had an associated tuberculosis.

4. Emphysema ranked second in percentage incidence. Right ventricular hypertrophy occurred in 28.9 per cent, and definite congestive failure in 22.3 per cent, of 45 uncomplicated cases.

6. The hearts of patients with pulmonary tuberculosis showed right ventricular hypertrophy in but 3.7 per cent, and definite congestive failure in 1.8 per cent, of 1,470 cases. The tuberculosis group had the lowest *percentage* of right ventricular hypertrophy of all chronic pulmonary disease groups, except chronic bronchitis. Nevertheless, due to the high incidence of tuberculosis, right ventricular hypertrophy was seen more frequently at autopsy in patients with tuberculosis than with any other pulmonary disease.

7. Cardiac hypertrophy, as evidenced by increased heart weights, was found to parallel closely the percentage of thickened right ventricular walls in the various chronic pulmonary disease groups.

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PHARMACOLOGY OF CHEYNE-STOKES RESPIRATION*

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CYCLIC respiration with periods of apnea and hyperpnea is most frequently encountered in association with cardiac disease, cerebral disturbances, spontaneous or traumatic, and with uremia. In cerebral accidents and uremia the respiratory disturbance is usually overshadowed by the other manifestations of the disease and ordinarily does not require consideration in therapy. In heart disease the cyclic breathing frequently results in great subjective distress, and, by interfering with the patient's rest and sleep, becomes a definite factor in preventing improvement of the cardiac state. In the more extreme cases the periodic breathing is continuous, and the patient is constantly disturbed by the repeated cycles of deep breathing. Continuous sleep is impossible, the exhausted patient dozing for a few seconds, only to be aroused by the deep breathing which follows the period of apnea. Under these conditions a patient may go for days without obtaining more than one minute's continuous sleep. Frequently, periodic breathing is the mechanism of nocturnal attacks of orthopnea and restlessness, preventing any prolonged period of continuous sleep.

Vogl, in 1927, first used theophylline with ethylenediamine (aminophyllin) in the treatment of cyclic breathing and reported the results of five years of observation in 1932.[1]

He concluded that periodic breathing and the associated subjective distress could be consistently abolished by intravenous administration of the drug. Others[2a, 2b] have confirmed the observations of Vogl. Although this action of aminophyllin is quite generally known, it is rather surprising that there are but few reports on the subject in the literature. The reports mentioned[2a, 2b] include studies of a small group of cases and are devoted mainly to speculation as to the possible mode of action of the drug. In this country this action of aminophyllin was mentioned by Smith and his associates,[3] in 1935. Other studies by the Iowa group are those of Paul, Greene, and Feller,[4] who showed that aminophyllin reduced the intravenous and intrathecal pressures in patients with Cheyne-Stokes breathing. The largest series of patients studied is that of Greene and Heeren,[5] in 1936, who carried out a systematic investigation which was controlled by graphic respiratory records. They studied a number of substances and found that complete abolition of the respiratory arrhythmia was observed only after the administration of amino-

*Read before the American Heart Association, San Francisco, Calif., June 10, 1938.
From the Department of Medicine, University of Southern California, Medical Service, Los Angeles County General Hospital.
Received for publication Nov. 15, 1938.

phyllin. In the report of the Council on Pharmacy and Chemistry of the American Medical Association, in 1930, on theobromine and theophylline compounds, no mention was made of any action on the respiration.[6] In a more recent report, in 1937, the statement made in discussing the action of aminophyllin on Cheyne-Stokes respiration is that "reports on such an action are for the most part uncritical and the observations are uncontrolled."[7] In the discussion of theophylline in two standard textbooks of pharmacology, Sollmann, 1937,[8] and Bastedo, 1938,[9] no mention is made of this action of theophylline. In 1937, Marais and McMichael[10] carried out a study on theophylline in Cheyne-Stokes breathing, concluding that the effective substance in aminophyllin is ethylenediamine and that theophylline itself is inactive.

The purpose of the present investigation was, first, to study in detail the action of aminophyllin and other drugs in Cheyne-Stokes breathing, and second, to repeat the studies of Marais and McMichael in order to establish more definitely what the active substance is. In the first series of cases graphic records were not made. In this group 0.24 gm. of the drug was administered intravenously in twelve patients, with restoration of normal breathing in eight. For comparison, coramine in 2 c.c. doses was administered to three patients who responded to aminophyllin. Coramine was without effect on the respiratory disturbance. In the second group, consisting of twenty-six patients, graphic respiratory records were made. Each record shows a control period, a period of drug administration, and a variable period following the administration of the drug. Of the twenty-six patients studied, twenty were suffering from varying degrees of cardiac decompensation associated with hypertension or coronary disease. Uremia was present in three instances and in three patients the cyclic breathing followed a cerebral accident. Forty-four observations were made, and the following drugs used: theophylline with ethylenediamine in eighteen patients, theophylline monoethanolamine in seven, ethylenediamine in five, benzedrine in three, caffeine sodiobenzoate in three, theophylline isopropanolamine in two, theophylline methylglucamine in two, and theophylline sodium acetate in four. Aminophyllin was administered in this series in doses of .48 gm. dissolved in 20 c.c. of water. This was injected intravenously, taking 3 to 5 minutes for the injection. Of the eighteen patients receiving aminophyllin, normal breathing was restored in sixteen. The drug failed in two instances. In one the respiratory disturbance was in a patient with coronary occlusion who died within a few hours. The second failure was in a case of massive cerebellar hemorrhage which caused death within a few hours. These results compare well with those of Greene and Heeren,[5] who were able to restore normal breathing in forty-five out of forty-nine trials. The effect of the drug was immediate in all instances, rhythmic breathing being established before the injection was completed (Figs. 1 and 2). During or shortly after the com-

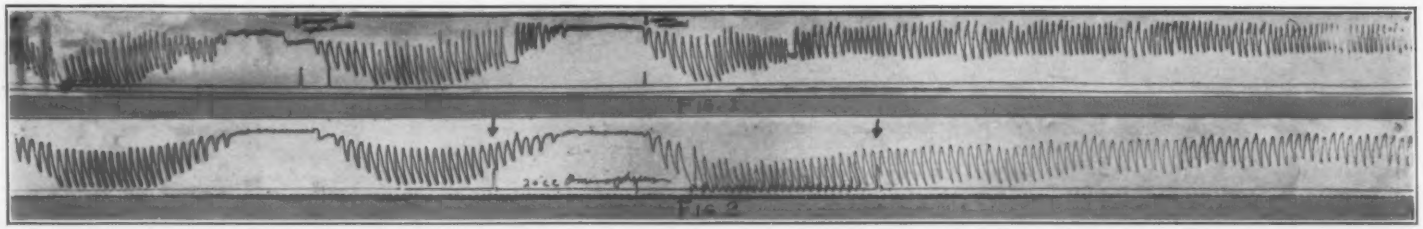

Fig. 1.—(Patient J. W.) Hypertensive heart disease. Respiratory record, showing the effect of an intravenous injection of 0.48 gm. of aminophyllin. Arrows show the start and finish of the injection. Note the complete disappearance of cyclic breathing. In all records, expiration is represented by the upstroke and inspiration by the downstroke. Note that with the disappearance of cyclic breathing the expiratory level is that of the apnea level.

Fig. 2.—(Patient A. K.) Hypertensive heart disease. Respiratory record, showing the effect of .48 gm. of aminophyllin intravenously. Arrows indicate the start and end of the injection.

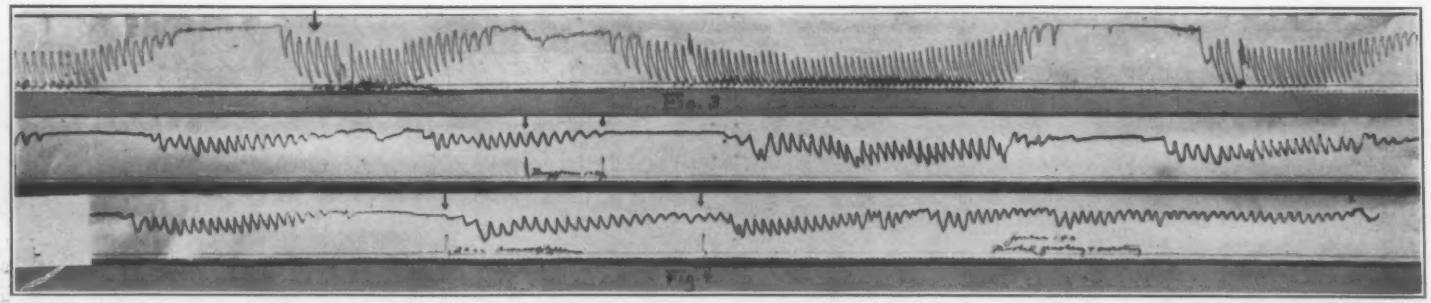

Fig. 3.—(Patient A. K.) Hypertensive heart disease. Respiratory record, showing the effect of the intravenous injection of 10 mg. of benzedrine sulphate. Injection started at arrow. Note the prolongation of the respiratory phase, without effect on the cyclic breathing. Fig. 2 shows the response of this patient to aminophyllin.

Fig. 4.—(Patient M. D.) Hypertension. Upper strip shows the continuance of cyclic breathing after the intravenous administration of 10 mg. of benzedrine sulphate. Lower strip shows the disappearance of cyclic breathing after .48 gm. of aminophyllin intravenously. Arrows indicate the beginning and end of the injection.

pletion of the injection there was usually a period of increased depth of breathing which was quickly followed by a reduction of the amplitude of the respirations. The duration of the effect varied from twenty minutes to a permanent restoration of normal breathing after a single injection. Most frequently the effect lasted from six to eight hours. In cardiac failure, the duration of the normal respiration appeared to depend on the severity of the failure, with a shorter duration in the more severe cases. However, even in patients with marked failure, the effect usually lasted for many hours.

Benzedrine is an adrenaline-like substance which has an intense stimulating action on the central nervous system.[11] There is no general agreement as to the underlying mechanism of Cheyne-Stokes breathing, but it has been frequently suggested that periodic respiration results from a depressed respiratory center. For this reason it was thought that the effect of a drug stimulating the central nervous system might be of interest. In three patients, 10 mg. of benzedrine sulphate were injected intravenously, and in no instance was the cyclic breathing abolished; in each case the injection was followed by one or two cycles of prolongation of the hyperpneic phase (Figs. 3 and 4). In each of the three patients failing to respond to benzedrine, aminophyllin abolished the cyclic breathing. Caffeine sodium benzoate in doses of 0.75 gm. was administered to three patients. In one case this was followed by normal breathing for 20 minutes. In the same patient aminophyllin restored normal respiration for several hours (Fig. 5). In two patients the drug had no effect on the respiratory disturbance, while aminophyllin showed its characteristic action.

Aminophyllin is theophylline with ethylenediamine, consisting of approximately 75 per cent theophylline and 25 per cent ethylenediamine. The drug was first introduced as a diuretic, in 1908, by Dessauer,[12] as a result of the search for a water-soluble theophylline compound for parenteral administration. Theophylline itself is relatively insoluble, and the double salt of theophylline with sodium acetate, soluble theocin, is soluble only in 25 parts of water. Theophylline with ethylenediamine is freely soluble in water, nonirritating, and easily forms a 40 per cent solution. At the outset it was considered that ethylenediamine was pharmacologically inert and played no part in the action of the theophylline compound. However, Vogl[1] reported a case in which cyclic breathing was abolished by ethylenediamine itself. Guggenheimer[2a] concluded that ethylenediamine increased the activity of theophylline. Grüter[2b] claimed that the combination of theophylline with ethylenediamine resulted in a more active diuretic substance than theophylline with other aliphatic amines. He also felt that ethylenediamine contributed to the coronary dilating action of aminophyllin. Marais and McMichael,[10] in 1937, came to the conclusion that the effect of aminophyllin in Cheyne-

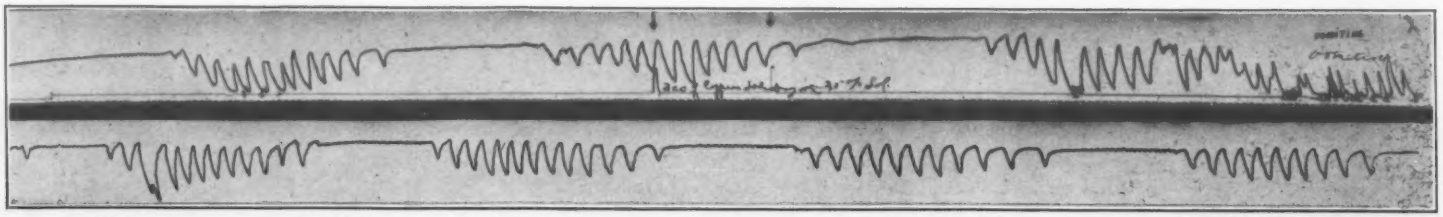

Fig. 5.—(Patient M. D.) Hypertension. This is a continuous record showing the ineffectiveness of .75 gm. of caffeine sodiobenzoate intravenously. Arrows indicate beginning, and end of injection. Fig. 4, lower strip, shows this patient's response to aminophyllin.

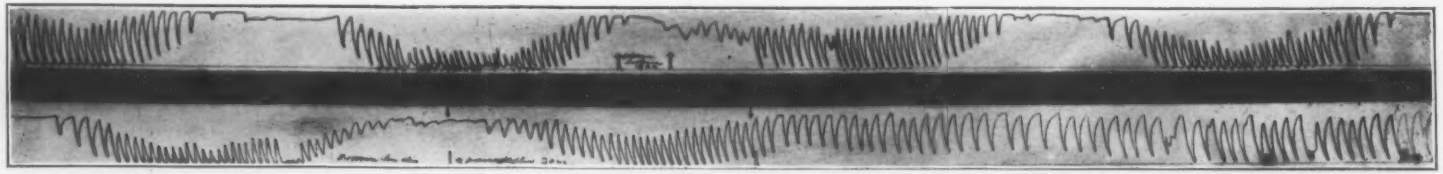

Fig. 6.—(Patient T. A.) Coronary thrombosis. Upper strip shows the continuance of cyclic breathing after the intravenous injection of 200 mg. of ethylenediamine. Lower strip shows the disappearance of cyclic breathing after .48 gm. of aminophyllin. Arrows indicate the start and end of the injection.

Stokes respiration was due mainly to its ethylenediamine component, and that theophylline itself was inactive. It seemed important to repeat this study, for if the amine were the active substance, a wide field for further pharmacologic study of cyclic breathing would be opened, as there is an almost unlimited number of related substances, many physiologically more active than ethylenediamine. In reviewing the report of Marais and McMichael it did not seem that their results were entirely convincing. The ethylenediamine was used in only three patients with Cheyne-Stokes breathing. The effect of the drug was of very short duration and was not at all comparable to the action of aminophyllin. In one case the ethylenediamine abolished the apneic phases, but periodic cyclic breathing still persisted. A subsequent injection of theophylline completed the restoration of normal rhythm. In the same patient, subsequently, only a transient abolition of periodic breathing was obtained with ethylenediamine, while aminophyllin abolished the cyclic breathing for two hours. In a third patient ethylenediamine restored normal respiratory rhythm. This was followed by theophylline, but the duration of the effect of both compounds was only fifteen minutes. At this time 0.48 gm. aminophyllin was injected, and the breathing was still regular twenty-two hours after the injection.

In the present study ethylenediamine was administered intravenously in 200 mg. doses to five patients. In one instance there was a very brief modification of the cyclic breathing; in the remaining four the drug was entirely without effect. Aminophyllin was then injected and was followed in each instance by its characteristic effect (Fig. 6). The effective dose of aminophyllin, 0.48 gm., contains approximately 125 mg. of ethylenediamine, so that the dose of ethylenediamine used was in excess of the amount present in an effective dose of aminophyllin. With the exception of Marais and McMichael,[10] who included some observations on the effect of theophylline sodium acetate, all observers have confined their investigations in Cheyne-Stokes respiration to theophylline with ethylenediamine. In order to study further the importance of the ethylenediamine fraction, the action of theophilline in combination with other amines was investigated. Theophylline with monoethanolamine was administered to seven patients with cessation of cyclic breathing in each instance. The onset and duration of the effect were similar to what was observed with aminophyllin (Fig. 7). Theophylline isopropanolamine and theophylline methylglucamine were administered to two patients, and the injection was followed by restoration of normal breathing in each case (Figs. 8 and 9). The question then arose whether the amine was at all necessary for this action, and therefore in four patients theophylline sodium acetate in doses of 0.66 gm. was administered, and this was also followed by the abolition of the cyclic breathing (Fig. 10). It should be

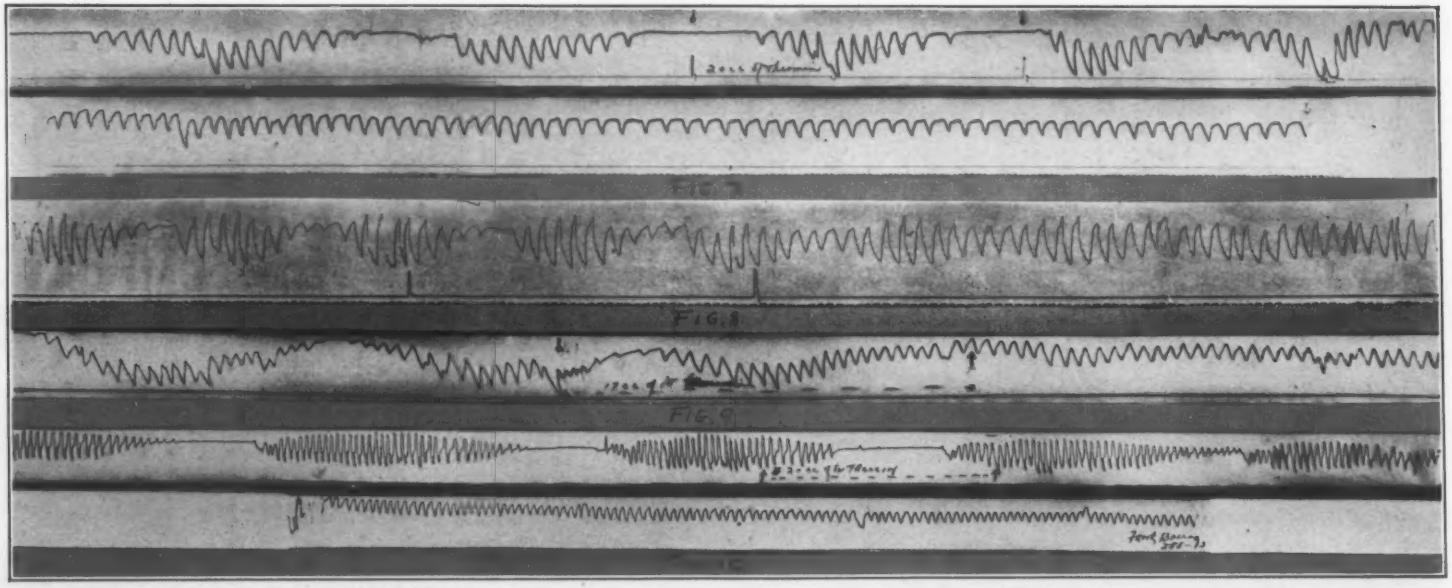

Fig. 7.—(Patient M. D.) Hypertension. Upper and lower strips form a continuous respiratory record, showing the effect of .48 gm. of theophyllin monoethamolamine. Note the disappearance of cyclic breathing. Figs. 4 and 5 show the ineffectiveness of benzedrine and caffeine sodiobenzoate in this patient.

Fig. 8.—(Patient J. S.) Hypertensive heart disease. Respiratory record, showing the effect of .48 gm. of theophyllin isopropanolamine intravenously. Note the disappearance of cyclic breathing.

Fig. 9.—(Patient J. A.) Cerebral thrombosis. Respiratory record, showing the effect of .4 gm. of theophyllin methylglucamine. Arrows indicate beginning and end of injection.

Fig. 10.—(Patient F. B.) Hypertension. Upper and lower strips form a continuous respiratory record showing the effect of .66 gm. of theophyllin sodium acetate intravenously. Arrows indicate the time of injection. Note the disappearance of cyclic breathing.

mentioned that in each instance in the above studies the amount of theophylline administered was approximately the same and was equivalent to the amount contained in 0.48 gm. of aminophyllin. It is felt that these observations indicate definitely that the ethylenediamine is of little importance in the action of the theophylline compounds and that the desired action may be obtained by theophylline in any combination.

MODE OF ACTION

The exact mechanism of the action of the theophylline compounds in Cheyne-Stokes respiration is not clear. This is not surprising, for there is no generally accepted explanation of the mechanism underlying cyclic breathing. There are several theories concerning the mode of action of the drug, but each is open to some objection. It has been suggested by Vogl[1] that the drug produces normal breathing by stimulating a depressed respiratory center. This concept is open to the objection that carbon dioxide, which is a powerful respiratory stimulant, does not reproduce the effect of theophylline in Cheyne-Stokes breathing.[5] Furthermore, such drugs as coramine and lobeline, which definitely stimulate an experimentally depressed respiratory center, are not effective in cyclic breathing. Greppi[13] demonstrated a rapid drop in spinal fluid pressure after the intravenous administration of aminophyllin in thirteen of sixteen individuals. He believed that this was most probably the result of the action of aminophyllin on the cerebral circulation. Paul, Greene, and Feller[4] found that aminophyllin reduced the intravenous and intrathecal pressures and suggested from these observations that cyclic breathing is abolished by an improvement in the cerebral circulation. Reduction in the cerebrospinal fluid pressure alone is apparently ineffective, for Greene and Heeren[5] found that the administration of 50 per cent glucose had no effect. Guggenheimer[2a] explained the action of aminophyllin on the basis of an increased cerebral circulation resulting from cerebral vasodilatation and improved cardiac action. He presents no experimental evidence to support this theory. It is evident that the cardiac effect of theophylline may be unimportant, because the drug is effective in periodic breathing unassociated with myocardial disease. The action of theophylline on the cerebral blood vessels has not been studied, but the related substance, caffeine, does produce cerebral vasodilatation.[14] It is quite clear from the present studies that the effect of the drug is not confined to the respiratory center. When theophylline compounds are administered to patients who are in a comatose state, there is a distinct tendency toward return of consciousness. This action is often very striking and suggests that the drug has a widespread effect on the central nervous system such as may be brought about by a general increase in cerebral blood flow. In this connection, it is interesting that benzedrine, which

apparently acts directly on the central nervous system in doses which have no circulatory effect, is without influence in cyclic breathing.

It must be concluded that the exact mode of action of theophyllin on Cheyne-Stokes breathing is not clear. A direct action on the respiratory center is extremely unlikely. The demonstration by Greppi[13] and by Paul and his associates[4] that a reduction in intrathecal pressure is produced by aminophyllin suggests that the drug acts on the cerebral circulation. It would seem that further progress may follow more direct studies on the action of the drug on the cerebral circulation.

PRACTICAL APPLICATION

One might question the practical value of therapy for Cheyne-Stokes respiration. In fact, in a recent volume by Fishberg,[15] the author states that "if one could abolish Cheyne-Stokes breathing, it is hardly of aid to the patient." This is entirely true in many instances when the respiratory disturbance is a terminal event. However, cyclic breathing with its attendant subjective distress may occur relatively early in the course of heart disease and, in some instances, the restoration of normal breathing gives not only subjective relief, but also by permitting the necessary rest is an aid in relieving cardiac failure. A dose of 0.24 gm. should be tried and, if this fails or if the duration of normal breathing is short, the larger dose of 0.48 gm. should be used. Of the thirty-three injections of the larger dose, unpleasant reactions followed in only a small number. These consisted of tachycardia, flushing of the face, sweating, and nausea.

The administration should be repeated when the cyclic breathing returns; usually not more than two or three doses a day are necessary.

In a small group of patients suffering from nocturnal respiratory distress, special enteric-coated tablets of a theophylline compound were administered by mouth. The dose was 0.6 gm. to 0.8 gm. in divided doses, given late in the day, usually 0.2 gm. doses at 6:00, 7:00, and 8:00 P.M. This was followed by good results in promoting restful sleep, making it possible to discontinue the use of sedatives.

CONCLUSIONS

Theophylline with ethylenediamine (aminophyllin) is a most effective drug in abolishing Cheyne-Stokes respiration.

The onset of the action is immediate, and the duration in the usual case is many hours, so that a dose of 0.48 gm. two or three times a day is sufficient to maintain rhythmic breathing.

The effective substance in aminophyllin is theophylline; ethylenediamine itself is ineffective; theophylline with other combinations shows its characteristic effect in Cheyne-Stokes breathing.

The following pharmaceutic houses gave generous supplies of their products: G. D. Searle and Company, Inc., theophylline ethylenediamine; Eli Lilly and Company, theophylline monoethanolamine; Abbott Laboratories, theophylline methylglucamine; The National Drug Company, theophylline isopropanolamine; Smith, Kline, and French Laboratories, benzedrine sulphate.

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AN ELECTROCARDIOGRAPHIC STUDY OF TWINS

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THE many investigations which have been made of the resemblances and differences of identical twins do not include extensive electrocardiographic studies. We have been interested in this subject not only as a biological problem, but as an aspect of the study of the individuality of the electrocardiogram. In particular, our purpose in this investigation has been twofold: first, to discover the degree of similarity or difference manifest in the electrocardiograms of twins, and second, to determine whether the identity or nonidentity of a given pair of twins can be decided from careful comparison of their electrocardiograms.

Weitz[1] (1925), reporting an extensive study of identical twins, mentioned that electrocardiograms were obtained from the majority of twins studied by him. These electrocardiograms were said to be readily separable into their proper pairs by inspection alone, but no specific data were given regarding the records. Almeida[2] (1929) secured electrocardiograms from a pair of twins who came under his observation. These electrocardiograms coincided when superimposed, which fact Almeida considered as additional evidence of the identity of these twins. Parade[3] (1935) reported an electrocardiographic study of ten pairs of identical twins. The records of five pairs of twins were closely alike; varying degrees of similarity or difference were found in the records of five other pairs.

The present study embraces thirty-two pairs of identical twins and eighteen pairs of nonidentical twins, a total of fifty pairs. The majority of these individuals were under 30 years of age. Careful histories were taken from forty-three of the fifty pairs of twins, to exclude possible etiological factors for heart disease; physical examination of the heart and lungs was made in this group. In order to bring out similarities or differences in the twins, notations were made of body build, height, weight, hair color, eye color, and left- or right-handedness. Inquiry was also made as to the frequency with which the twins had been confused. A brief evaluation was taken of resemblance or difference in personality make-up. The final impression as to identity or nonidentity of the twins was established on the basis of all the data collected regarding each pair of twins.

The age, sex, height, and weight of the majority of the twins studied were as follows (Table I), including fifty-eight of the sixty-four identical twins and twenty-one of the thirty-six nonidentical twins.

With the cooperation of Wellford C. Reed, William H. Gordon, and William Paul Thompson.

From the Cardiac Clinic of the Massachusetts General Hospital, Boston.

Received for publication Nov. 11, 1938.

TABLE I

IDENTICAL TWINS

TWIN	AGE	SEX	HEIGHT (INCHES)	WEIGHT (POUNDS)
G.	47	F	66.7	145.0
H.			65.0	143.5
W.	25	M	69.0	153.0
J.			69.0	150.0
P.	21	F	61.5	125.5
H.			60.6	119.0
D.	27	F	66.8	148.0
E.			66.5	140.5
S.	34	M	70.2	155.3
G.			70.1	155.3
V.	22	F	64.0	120.5
G.			64.8	119.3
V.	21	M	70.5	156.0
J.			70.1	156.0
Dor.	21	F	63.5	106.0
Do.			63.5	111.0
Jo.	15	F	64.7	129.8
Je.			66.5	125.0
A.	21	M	64.5	135.3
M.			65.0	136.8
H.	21	F	65.0	113.0
G.			65.0	120.5
Ba.	21	F	62.0	123.0
Be.			61.0	119.0
T.	17	F	61.9	126.5
I.			62.2	119.0
H.	20	F	64.0	127.0
E.			64.5	129.0
A.	21	M	66.8	144.0
J.			69.0	148.3
L.	22	F	63.5	110.0
F.			62.1	109.0
W.	21	M	65.0	132.0
F.			65.7	140.8
M.	32	F	65.3	131.3
C.			64.8	148.5
A.	22	F	62.5	136.0
J.			63.0	139.8
N.	19	F	63.5	133.0
P.			63.5	127.0
E.	21	F	61.5	151.5
I.			62.0	109.0
Ca.	27	F	64.3	137.0
Cb.			63.5	123.0
D.	26	F	59.0	88.5
G.			59.0	91.0
D.	41	F	65.3	119.5
K.			65.3	123.0
F.	19	F	66.0	125.5
P.			66.0	130.0
A.	35	F	64.0	136.0
E.			65.0	141.0
G.	22	M	69.5	157.0
L.			69.5	157.0
V.	23	F	67.0	137.0
F.			67.0	134.5
W.	22	M	66.0	132.0
B.			66.0	130.3

TABLE II

NONIDENTICAL TWINS

TWIN	AGE	SEX	HEIGHT (INCHES)	WEIGHT (POUNDS)
M.	22	F	67.5	131.0
M.			69.5	147.0
R.	22	M	62.5	130.0
V.			63.5	120.0
Mi.	6	F	43.5	45.5
Ma.			44.5	45.0
H.	21	M	65.8	124.3
A.			63.7	128.7
A.	21	F	59.9	179.8
V.			59.9	132.5
Ru.	21	F	64.6	118.8
Ro.			61.4	101.2
H.	21	F	64.5	112.0
G.			63.0	118.5
C.	23	M	72.0	158.0
J.			70.8	194.0
V.	19	F	65.3	151.0
E.			65.3	142.0
M.	21	F	69.0	136.0
J.			69.5	141.0
F.	21	M	67.5	136.0
S.		M	69.0	135.0

All of the individuals in this series were considered to have normal hearts with the exception of one, who had evidence of mitral stenosis on physical examination, but had no cardiac symptoms. The electrocardiograms of two pairs of twins exhibited low T waves in the conventional leads. The electrocardiograms of another pair of twins (aged 21 years) showed inverted T waves in the precordial leads. The remainder of the electrocardiograms of the twins were well within the usual normal limits.

In deciding the measure of similarity shown in the electrocardiograms of the twins studied, not only has the character of the deflections been considered, but also their amplitude. The electrocardiograms of both identical and nonidentical twins have been conveniently grouped as showing "close similarity," "some similarity," "no similarity." The absolute criteria for such designations have been established from comparison of the amplitudes of the deflections, especially of the QRS waves, in the conventional leads. Electrocardiograms classed as showing "close similarity" are those which exhibit differences in the amplitude of similarly shaped QRS deflections of not more than 3 mm. in any conventional lead. Those records classed as having "some similarity" show differences in the amplitudes of the QRS deflections greater than 3 mm., but not exceeding 5 mm., in any classical lead. All electrocardiograms of twins which show differences in the amplitudes of the QRS deflections greater than 5 mm. in any lead are considered to show "no similarity"; such records are almost always dissimilar in shape as well as in size. The differences in the amplitudes of the QRS deflec-

tions of the precordial leads are not comparable to those found in the conventional leads and are considered mainly due to variations in the position of the precordial electrodes. For this reason the criteria for classification of the electrocardiograms of the twins, as applied to the conventional leads, do not include the precordial leads. The P and T waves which vary in amplitude between narrow limits in the electrocardiograms of twins have been found to show only slight differences in any lead, making it unnecessary to consider these deflections in establishing criteria for the grouping of the records.

TABLE III

ELECTROCARDIOGRAMS

TYPE OF TWINS	NUMBER OF CASES	CLOSE SIMILARITY	SOME SIMILARITY	NO SIMILARITY
Identical	32	16 (50%)	8 (25%)	8 (25%)
Nonidentical	18	4 (22%)	5 (28%)	9 (50%)

ELECTROCARDIOGRAMS OF IDENTICAL TWINS

Of the thirty-two pairs of identical twins studied, the electrocardiograms of sixteen pairs of twins have been found to show "close similarity"; the records of eight other pairs show "no similarity." Among the electrocardiograms showing "close similarity," the first leads are most nearly identical, and the maximal differences are found in Lead III and in the precordial lead. The variations found in Lead III cannot be strictly correlated with the differences in weight of two to six pounds which existed between some individuals in this group, although differences in the height of the diaphragm may be of some importance.

The following are examples of the different degrees of similarity found to exist among the electrocardiograms of the identical twins.

ELECTROCARDIOGRAMS SHOWING CLOSE SIMILARITY

V. and J. C. are young men, 21 years of age, who are very much alike in appearance. It is of particular interest that both were refused army enlistment in 1936 because of albuminuria. Subsequently they were studied at the Boston City Hospital and found to have orthostatic albuminuria.[4] It is said that while they were in the hospital they were constantly being confused, one for the other, by the ward staff. Their chief physical and electrocardiographic characteristics are given in Tables IV and V.

TABLE IV

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Sandy	Blue	Right	70.5	156
J.	Sandy	Blue	Right	70.1	156

TABLE V

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+Trace	+2.0, -2.0	+1.5
	J.	+Trace	+3.0, -2.0	+2.0
II	V.	+1.5	-0.5, +11.0, -2.5	+2.0
	J.	+1.0+	-1.5, +11.0, -1.5	+2.5
III	V.	+1.0+	-2.0, +13.0, -2.0	+0.5
	J.	+1.0	-2.0, +10.5, -0.5	+0.5
IV	V.	+0.5	-6.0, +20.0	-4.5
	J.	+Trace	-5.0, +8.0	-5.0

ELECTROCARDIOGRAMS SHOWING SOME SIMILARITY

V. and F. D. are female graduate students, 23 years of age, who look alike and are often mistaken for each other. In temperament they are very much alike. Their chief physical and electrocardiographic characteristics are given in Tables VI and VII.

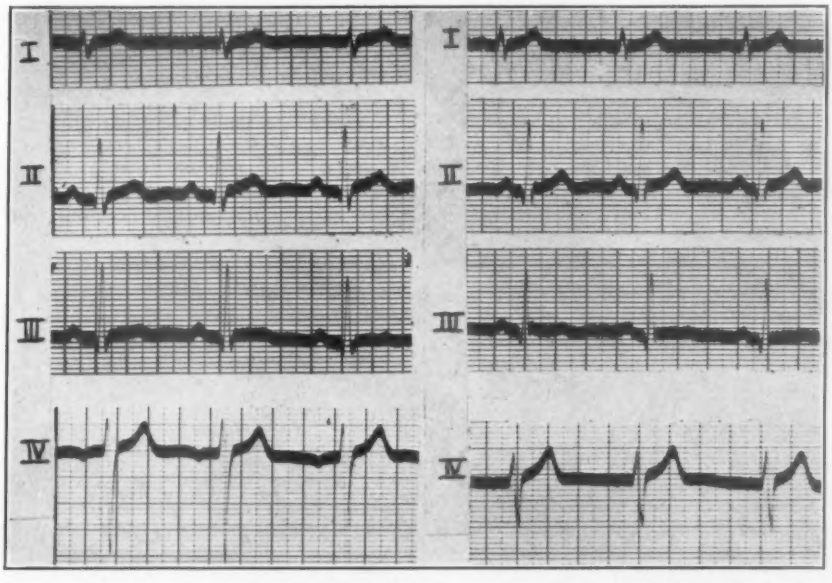

Fig. 1.—Electrocardiograms of identical twins V. and J. C., showing "close similarity" (left, V.; right, J.).

TABLE VI

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Blond	Hazel	Right	67.0	137.0
F.	Blond	Hazel	Right	67.0	134.5

ELECTROCARDIOGRAMS SHOWING NO SIMILARITY

G. and H. G. are female stenographers, 21 years of age, who are very much alike in appearance and are occasionally mistaken for each other. Their main physical and electrocardiographic characteristics are given in Tables VIII and IX.

TABLE VII

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+0.5	+1.0, -1.0	+1.0
	F.	+0.5	+3.0, -1.0	+2.0
II	V.	+1.0	-1.0, +14.0	+1.5
	F.	+1.0	-1.0, +16.0	+1.5
III	V.	+ trace	-2.5, +16.0	diphasic trace
	F.	+ trace	-1.0, +11.0	-1.0
IV	V.	+1.0	+16.0, -2.0	+2.5
	F.	+1.5	-1.0, +18.0	+2.0

TABLE VIII

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
G.	Brown	Blue	Right	65.0	120.5
H.	Brown	Blue	Right	65.0	113.0

TABLE IX

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	G.	+0.5	+2.5, -5.0	+1.0
	H.	+0.5	-0.5, +7.0, -2.0	+1.5
II	G.	+1.0	-trace, +11.0, -2.0	+1.5
	H.	+1.0	+10.0, -trace	+2.0
III	G.	+1.0	-1.0, +13.0	+1.0
	H.	+0.5	+3.0	+0.5
IV	G.	+1.0	+11.0, -6.0	+2.0
	H.	+0.5	+10.0, -4.0	+3.5

ELECTROCARDIOGRAMS OF THE NONIDENTICAL TWINS STUDIED

Of the eighteen pairs of nonidentical twins studied according to the criteria already mentioned, the electrocardiograms of four pairs have been found to show "close similarity." The records of five pairs showed "some similarity," and the records of nine pairs showed "no similarity." As was found in the electrocardiograms of the identical twins, the closest resemblance exists in the first leads, and the maximal differences are found in Lead III and in the precordial leads. Likewise, the P and T waves show only minimal differences regardless of the degree of similarity exhibited in the QRS waves. The following illustrate the findings in nonidentical twins.

ELECTROCARDIOGRAMS SHOWING CLOSE SIMILARITY

Ru. and Ro. D. are young women, 21 years of age, who differ markedly in body build and in general appearance, as is illustrated in Table X. Their personality make-ups are entirely different. Table XI gives their significant electrocardiographic findings.

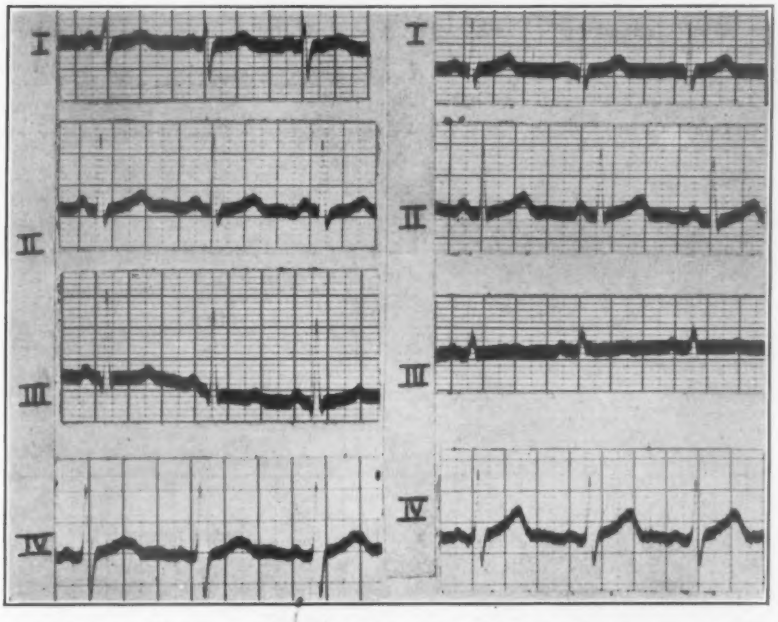

Fig. 2.—Electrocardiograms of identical twins G. and H. G., showing "no similarity" (left, G.; right, H.).

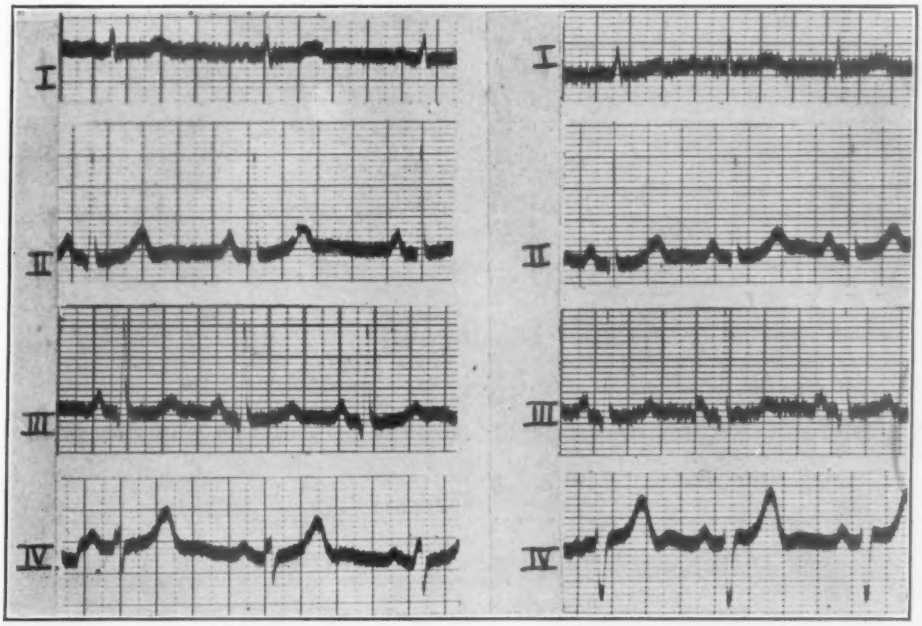

Fig. 3.—Electrocardiograms of nonidentical twins Ru. and Ro. D., showing "close similarity" (left, Ru.; right, Ro.).

TABLE X

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
Ru.	Brown	Blue green	Right	65	119
Ro	Dark brown	Hazel	Right	61	99

TABLE XI

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	Ru.	+ trace	+3.0	+1.0
	Ro.	+ trace	+3.5	+1.0
II	Ru.	+2.5	−trace, +16.0	+4.0
	Ro.	+2.0	−trace, +16.0	+3.5
III	Ru.	+2.0	−1.5, +15.0	+2.0
	Ro.	+2.0	−1.5, +16.0	+2.0
IV	Ru.	+1.5	+2.5, −4.0	+5.5
	Ro.	+2.0	+1.5, −9.0	+8.0

ELECTROCARDIOGRAMS SHOWING SOME SIMILARITY

F. and S. B. are male college students, 21 years of age, who do not resemble one another in appearance, and say that their personality make-ups are entirely unlike. Their physical and electrocardiographic characteristics, in brief, are given in Tables XII and XIII.

TABLE XII

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
F.	Brown	Green	Left	67.5	136
S.	Light brown	Blue-green	Right	69.0	135

TABLE XIII

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	F.	+trace	+3.5, −1.0	+2.5
	S.	+0.5	+5.0, −1.5	+3.0
II	F.	+1.5	−trace, +14.0	+3.5
	S.	+1.0	−2.0, +18.0, −1.5	+4.0
III	F.	+1.0	+12.0	+1.5
	S.	+1.0	−2.0, +14.0	+1.5
IV	F.	+1.0	−trace, +18.0, −2.0	+5.0
	S.	+1.0	−2.0, +22.0, −2.0	+5.5

TABLE XIV

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Brown	Brown	Right	59.9	132.5
A.	Brown	Brown	Right	59.9	179.5

ELECTROCARDIOGRAMS SHOWING NO SIMILARITY

V. and A. C. are young women, aged 21 years, quite different in physique and in general appearance, and never mistaken for each other. Tables XIV and XV show their chief physical and electrocardiographic characteristics.

TABLE XV

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+1.0	+5.0, −1.5	+2.0
	A.	+1.5	−trace, +11.0, −4.5	+3.0
II	V.	+1.0	−1.0, +14.0, −2.0	+3.0
	A.	+1.5	+11.0, −4.0	+3.0
III	V.	+0.5	−2.0, +12.0, −1.0	+0.5
	A.	−0.5	+1.0, −2.0, +3.0, −2.0	−0.5
IV	V.	+0.5	+10.0, −3.0	+1.5
	A.	+0.5	+14.0, −7.0	+2.0

DISCUSSION

The electrocardiograms of the twins studied have been found to show no such close degree of similarity as to permit exact superimposition of the records. The same degree of similarity or difference as may be found in the electrocardiograms of a pair of identical twins may also exist in the records of a pair of nonidentical twins, which fact precludes the determination of the identity or nonidentity of a given pair of twins from their electrocardiograms. The differences found in the electrocardiograms of identical twins cannot be strictly correlated with small differences in heights or weights, for differences of the same order are found in the electrocardiograms of identical twins of the same heights and weights. Furthermore, electrocardiograms of nonidentical twins differing markedly in body build may show close similarity. These findings are considered to illustrate the individuality of the electrocardiogram.

Our findings do indicate, however, that a close degree of similarity is more often to be found in the electrocardiograms of identical twins than in the electrocardiograms of nonidentical twins; the ratios in our series were 16:32 and 4:18, respectively.

During the course of this investigation a simultaneous orthodiagraphic and fluoroscopic study was made of the hearts of twins. The results are presented in a separate report.[5]

CONCLUSIONS

An electrocardiographic study has been made of thirty-two pairs of identical twins and eighteen pairs of nonidentical twins. Varying degrees of similarity or difference have been found in the electrocardiograms of all the twins studied. Close similarity or no similarity

may be found in the electrocardiograms of both identical and nonidentical twins, for which reason the identity or nonidentity of a given pair of twins cannot be determined from study of their electrocardiograms alone, although identical twins did show a higher percentage of similar electrocardiograms than did nonidentical twins (ratio of 16 to 32, compared to that of 4 to 18). The lack of absolute correspondence of the electrocardiograms of identical twins of the same height and weight emphasizes the individuality of the electrocardiogram.

Addendum.—Since the completion of this report an extensive electrocardiographic study of 106 pairs of twins has been published by Parade and Lehmann (Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **22**: 96, 1938). Their results, using criteria similar to our own, are as follows:

ELECTROCARDIOGRAMS

TYPE OF TWINS	CLOSE SIMILARITY	SOME SIMILARITY	NO SIMILARITY
Identical	22 (41.5%)	25 (47.2%)	6 (11.3%)
Nonidentical	1 (1.9%)	19 (35.8%)	33 (62.3%)

These results, as well as others cited by Parade and Lehmann, are in general accord with our conclusions.

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THE PROBLEM OF ANGINA PECTORIS IN THE NEGRO*

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THERE are numerous comments in the literature on the rarity of angina pectoris in the negro.[1, 2, 3, 4, 5, 6] Most clinicians in the southern part of the United States are in accord that it is infrequently encountered in this race. Does the infrequency of angina pectoris in the negro indicate a white racial susceptibility to the disease? Roberts[4] attributes the difference in incidence to the lack of mental stress and strain in the negro. Schwab and Schulze[5] believe that it is due to an inherent difference in the sensitivity of the nervous systems in the two races. In a recent study, however, of the clinical manifestations of essential hypertension among negroes and whites admitted to the wards of the Louisville City Hospital,[7] we found that angina pectoris was uncommon in both races. A history of angina pectoris was obtained in 0.5 per cent of the negro and only 1.5 per cent of the white patients.

Uncomplicated angina pectoris, of course, does not often require hospitalization. Moreover, the myocardial, cerebral, and renal failure symptoms of the hospitalized patient could obscure all history of cardiac pain. For these reasons it was decided to study the incidence of angina pectoris in negro patients with essential hypertension attending the outpatient department of the Louisville City Hospital, using, for comparison, a group of white patients with hypertension admitted to the clinic during the same period. This municipal clinic accepts only ambulatory and absolutely indigent individuals. Most of the clientele of the clinic are in the lowest intellectual and social scale of life. Patients with essential hypertension were selected for study because of the high incidence of angina pectoris in association with this disease.

The records of 324 negroes with essential hypertension, including only adults over 20 years of age, who were admitted consecutively to the outpatient department, were analyzed and compared with those of 246 white patients admitted to the clinic during the same period. Table I shows the age and sex distribution of the patients. There were 137 negro men, 187 negro women, 132 white men, and 114 white women. A history of angina pectoris was obtained in 9, or 2.8 per cent, of the negroes, and in 12, or 4.8 per cent, of the white patients. There were 3 negro males, 6 negro females, 8 white males, and 4

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Received for publication Nov. 12, 1938.

white females with the syndrome. Thus the incidence was low in both races. These figures are comparable to those reported by Flaxman,[8] who found angina pectoris in 2.5 per cent of 430 white patients and 0.5 per cent of 193 negro patients with hypertensive heart disease in the various charity wards and clinics in Chicago. In contrast is the reported incidence in private patients. White[9] obtained a history of angina pectoris in 26 per cent, and Nuzum, Elliot, and Evans[10] in 12 per cent of persons with essential hypertension encountered in private practice.

TABLE I

AGE AND SEX DISTRIBUTION OF OUTPATIENTS WITH ESSENTIAL HYPERTENSION IN NEGRO AND WHITE RACES

AGE	NEGROES (324 CASES)			WHITES (246 CASES)		
	M	F	TOTAL	M	F	TOTAL
20-29	1	3	4			
30-39	9	30	39	3	8	11
40-49	27	54	81	11	16	27
50-59	50	65	115	41	47	88
60-69	30	29	59	53	32	85
70-79	18	6	24	22	10	32
80-89	2		2	2	1	3
	137	187	324	132	114	246

It is noteworthy that when the incidence of angina pectoris is low in the negro it is similarly low in the white patients from the same clinic. Stone and Vanzant,[2] who did not find a single instance of angina pectoris in negroes with heart disease, state that it is likewise not seen very frequently in the whites who attend the charity clinic, whereas among private patients it is fairly common. Gager,[11] in his private patients with heart disease, found that 10.9 per cent had angina, in contrast with 5.4 per cent in his charity practice. In the negro group of charity patients the incidence of angina was 4.5 per cent.

It is also noteworthy that in the literature on angina pectoris there are numerous comments on the comparative infrequency with which it is encountered in charity patients. Allbutt[12] states: "In my experience, its incidence among the laboring classes in Leeds was not remarkably high." Osler[13] comments: "Though occurring among the poor, it is more frequently met with among the rich, or in persons of easy circumstances." Gallavardin[14] claims that professional and well-to-do people are more frequently affected. Recent reports on relatively large numbers of cases, such as that of White and Bland,[15] and Brooks,[16] are based entirely on private patients. Czyhlarz[17] feels that this social difference in the incidence of the disease can be explained on a difference in sensitivity of nervous systems. Hamman[18] believes that angina pectoris will always be a disease of the refined, intellectual classes, since its effects are keenly appreciated and fluently

described by the intellectually alert, but not clearly perceived or described by the intellectually obtuse.

A disparity in the incidence of angina pectoris in the white and colored races might be explained on a difference in associated pathologic changes. Studies on the racial incidence of coronary artery disease would indicate that marked coronary sclerosis is not as common in the negro as in the white race. Thus, Bruenn, Turner, and Levy[19] found that 133 of 137 cases of advanced coronary sclerosis occurred in white persons, and only 4 in negroes, although the ratio of white to negro patients studied was 12 to 1. A study by Johnson[20] of the autopsy records of 400 patients more than 39 years of age showed that the incidence of marked coronary sclerosis was 24 per cent for white males, 9 per cent of negro males, 10 per cent for white females, and 4 per cent for negro females. From this he concluded that members of the white race are much more susceptible to coronary sclerosis than negroes.

Neither of these reports considered the incidence of hypertension in the cases studied, a factor which would materially influence the relative severity of coronary disease. With this factor in mind, an analysis was made of the macroscopic descriptions of the coronary vessels in the protocols of 177 negro and 178 white patients with essential hypertension who were autopsied at the Louisville City Hospital from 1930 through 1936. Table II shows the distribution of the cases as to race, age, and sex. Males predominated in both races, probably because of the relative ease with which permission can be obtained for an autopsy on a man. No patient in either race was less than 30 years of age. There was a greater incidence in the younger age groups of the negroes than in the whites.

TABLE II

AGE AND SEX DISTRIBUTION OF AUTOPSY CASES OF ESSENTIAL HYPERTENSION IN NEGRO AND WHITE RACES

AGE	NEGRO (177 CASES)			WHITE (178 CASES)		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
30-39	11	10	21	3		3
40-49	22	13	35	12	8	20
50-59	30	27	57	17	19	36
60-69	24	10	34	48	14	62
70-79	10	11	21	29	15	44
80-89	6	3	9	11	2	13
	103	74	177	120	58	178

Table III shows the incidence of severe coronary sclerosis and myocardial infarction in each race. Marked coronary sclerosis was found in 20 per cent of the negro males, 21 per cent of the white males, 31 per cent of the negro females, and 24 per cent of the white females. Over 7 per cent of the negroes had myocardial infarction, in contrast to 10 per cent for the whites. This indicates that there is no racial

difference in the incidence of advanced degrees of coronary sclerosis or of myocardial infarction in individuals with essential hypertension. Hence differing degrees of coronary disease cannot explain the disparity in the incidence of angina in the negro as compared with the white race.

TABLE III

INCIDENCE OF MYOCARDIAL INFARCTION AND SEVERE CORONARY SCLEROSIS IN AUTOPSY CASES OF ESSENTIAL HYPERTENSION, COLORED CONTRASTED WITH WHITE RACE

AGE	NEGRO				WHITE			
	SEVERE CORONARY SCLEROSIS		MYOCARDIAL INFARCTION		SEVERE CORONARY SCLEROSIS		MYOCARDIAL INFARCTION	
	M	F	M	F	M	F	M	F
30-39		1			1			
40-49	6	4	2		2	1		
50-59	5	9	3	2	2	4	2	1
60-69	6	4	5		12	1	4	5
70-79	2	4	1		6	7	6	
80-89	2	1			3	1	1	
	21	23	11	2	26	14	13	6

DISCUSSION

Explanations of the rarity of angina pectoris in the negro are inadequate because they do not take into account the fact that there is a similar low incidence in white patients who are of the same intellectual level. A lack of ability to fully describe and interpret the sensation of cardiac pain can entirely explain the infrequency with which the syndrome is encountered in the negro. This is the same explanation offered by Hamman[18] to account for the social differences in the incidence of angina pectoris. It is of interest that the most satisfactory histories of angina in this study were obtained from patients who were above the intellectual level of the average patient attending the outpatient department. The economic depression necessitated their admission to a free clinic. Differences from the white race in susceptibility to mental strain, nervous system sensitivity, or pathologic changes in the heart do not furnish an adequate explanation. Such factors explain the absence of the syndrome in certain individuals in a homogeneous group, but they cannot account for the large difference in the incidence in negro charity patients and white private patients. While a disturbed emotional state can precipitate an anginal attack, a more than moronic intelligence is required to describe that attack. We do not find angina pectoris in the negro because he is unable to give an adequate description of the sensations which the attack produces. Every clinician knows how difficult it is to obtain a good history from a southern negro. A difference in nervous system sensitivity seems a plausible explanation. However, the negro is very susceptible to pain. Moreover, both white and negro patients who attend the same clinic cannot have a low threshold for

those stimuli, such as effort, cold, mental strain, and excitement, which precipitate an anginal attack in an intelligent white person.

SUMMARY

1. A study is presented of the problem of the relative infrequency of angina pectoris in the ambulatory negro with essential hypertension.

2. The incidence of angina pectoris is low in both negro and white patients with hypertension who attend the same outpatient clinic. The syndrome occurred in 2.8 per cent of 314 negro patients and 4.8 per cent of 246 white patients with essential hypertension.

3. No racial difference in the incidence of advanced degrees of coronary sclerosis or myocardial infarction in individuals with essential hypertension was found at autopsy.

4. A lack of ability to fully describe and interpret the sensation of cardiac pain can entirely explain the relative infrequency with which angina pectoris is encountered in the negro charity patient as compared with the white private patient.

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ABSENCE OF PULSE IN THE VESSELS OF THE UPPER EXTREMITIES AND NECK IN ANEURYSM OF THE AORTIC ARCH

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THE complete absence of pulsation in the radial, brachial, and carotid arteries bilaterally is a rare condition. Two patients presenting such abnormalities have been under observation and subsequently have come to autopsy in the Cincinnati General Hospital. A study of the literature reveals that just five similar cases of pulse absence in aortic aneurysm have been reported previously and that in only three of these was there a post-mortem examination.

Hare and Holder,[1] in 1899, analyzing 953 cases of aortic aneurysm with special reference to pulse abnormalities, found that in only thirty-two out of 784 cases of aneurysm of the aortic arch was there any pulse abnormality at all, and in only five of these was there complete absence of the radial pulse on one side. In the large series of 4,000 cases collected and reviewed by Boyd,[2] in 1924, no case of complete absence of carotid or radial pulse was recorded. In the literature of the past twenty years, including the articles by Findlay, [3] Arnold,[4] and Kahn,[5] much space has been given to the consideration of pulse inequalities, but little mention has been made of such observations as are under discussion here. The only exception to the general lack of discussion of absence of arterial pulsation is Osler's[6] mention of a reported case of complete obliteration of the pulse in the arteries of the head and upper extremities in a patient with a large aneurysm of the arch of the aorta. Furthermore, it should not go unnoticed that Osler[7] mentions an instance of obliteration of the pulse in the abdominal aorta and in both lower extremities in the presence of aneurysm of the abdominal aorta.

According to Hirschfelder, Harvey was the first to report obliteration of the pulse in aneurysm of the thoracic aorta. Subsequently, throughout the literature inequality and retardation of the pulses were frequently referred to, while complete obliteration was seldom described. Lamb,[8] in 1920, for instance, in an analysis of ninety-two history records, reported thirteen cases in which there was inequality of pulses, and later, in 1924, Dr. Morris H. Kahn[5] published a treatise and case report dealing with delayed radial pulses in aortic aneurysm.

Cohen and Danie,[9] in 1933, when reporting their own case of bilateral pulse absence in aortic aneurysm, made mention of only four similar re-

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Acknowledgment is made to the Department of Medicine, Cincinnati General Hospital, for the use of clinical records.

Received for publication Nov. 16, 1938.

ports in the literature. In but two of these cases were post-mortem examinations performed. The first report, that of Broadbent[10] (1875), described the absence of both radial pulses and of the right carotid pulse, all of which was accounted for by a plaque of atheroma almost completely obliterating the orifice of the innominate artery, which was unusually close to the left common carotid artery. An anomalous vertebral artery, arising directly from the aortic arch, encroached upon the orifice of the left subclavian artery, which likewise was further narrowed by an atheromatous plaque. The lesions therefore were multiple.

In the second case, reported by Shikhare,[11] in 1921, there was absence of the pulses as a result of almost complete obliteration of the lumina of the large vessels arising from the aortic arch by ante-mortem thrombi, which arose as fingerlike projections from a "mother" clot filling the greater portion of the dilated aortic arch.

In the two remaining cases, those of Crawford[12] and Kampmeier and Neumann,[13] there was no post-mortem examination, so that the pathologic basis for the obliteration of the pulses necessarily remained a matter of conjecture. It was suggested, however, by Kampmeier and Neumann that in Crawford's case, as well as in their own, the obliteration of the arterial pulses was probably produced by pressure of an enlarging aneurysmal sac on the arterial trunks.

In Cohen and Danie's[9] own case of bilaterally absent carotid and radial pulses, post-mortem examination disclosed a fusiform aneurysm of the ascending and transverse "arms" of the thoracic aorta, with complete obliteration of the three main arteries arising from the aortic arch, their sites being represented merely by two shallow depressions. Microscopic examination of sections taken through the sites of occlusion showed extensive subintimal proliferation in the innominate, left subclavian, and left carotid arteries. Although syphilitic endarteritis is admittedly rare in large arteries, these investigators ventured the opinion that occlusion of the large vessels came about through narrowing of their orifices by plaques associated with syphilitic subintimal proliferation.

The first case here reported was recently observed in the Cincinnati General Hospital. It was of unusual interest because of the absence of pulsations in the superficial arteries of the right arm and both carotids, and of importance in that the pathologic findings were different from any so far recorded. Interest being aroused as to the incidence of this unusual condition, the clinical and necropsy records of all patients coming to post mortem in the Cincinnati General Hospital during the past eleven years, 1927 to 1937, inclusive, were reviewed. In a total of 7,455 autopsies performed during this period, 113 cases of aneurysm of the aortic arch were encountered, in five of which there was complete absence of pulse in one or more of the superficial vessels of

the upper extremity and neck. In two there were pulse differences only in the upper extremities, and in the entire series only one case was discovered in which there were no recognizable pulsations in the radial and carotid vessels bilaterally. This is included as Case 2 of the present report.

REPORT OF CASES

CASE 1.—*History:* M. J., 65 years of age, a colored woman, was brought to the Cincinnati General Hospital, Feb. 3, 1938, unaccompanied by either relatives or friends. On admission to the receiving ward the patient could give no history, for she was unable to talk; her entire right side was paralyzed. The history, therefore, necessarily was obtained subsequently from a woman with whom the patient had been residing during the past year. According to this informant, the patient had always enjoyed fair health until Jan. 24, 1937, when, while sitting in a chair, she suddenly slumped forward, and on being examined immediately thereafter was found to be without the power of speech and paralyzed over her entire right side. The patient was placed in bed, and the following morning could respond to questions and make active movements with her right arm and leg. Following this episode she was again up and about until Feb. 2, 1938, the day before admission, when again, while sitting in a chair, she suddenly fell to the floor unconscious, was again put to bed; the following day, on advice of a local physician, she was brought to the hospital. No further history was obtainable.

Examination.—Physical examination, a short time after admission on the neurologic ward, revealed an aged, semiconscious, thin, little colored woman who was unable to talk or to move her right arm and leg. Her head was retracted laterally to the left and the neck became rigid when forceful flexion to the right was attempted. The right margin of the mouth drooped downward, the right side of the body was flaccid, the left arm and hand moved spasmodically, and the left leg was flexed on the thigh. The only obtainable response to external stimuli was a withdrawal movement of the left upper and lower extremities following pinprick. Respirations were Cheyne-Stokes in character, labored and noisy. The skin generally was dry, scaly, and much warmer over the left side of the body.

Cursory examination of the head revealed no evidences of recent or past trauma. The pupils were equal, regular, moderately dilated, and reacted well to light and in accommodation. No nystagmus or strabismus was noted. Ophthalmoscopic examination showed the disks to be clearly outlined and without papilledema. There were well-marked, bilateral, retinal arteriosclerosis and notching of veins by arteries which crossed them.

The right margin of the mouth dropped and the left lip was full and relaxed. The lower jaw was edentulous, the pharynx was clear, and the tongue deviated to the left of the midline.

There was a torticollis deformity on the left, with prominence of the right sternocleidomastoid muscle and complete absence of pulsations in both carotid vessels.

The chest was symmetrical and the respiratory excursions equal, jerky, and variable. A few dilated veins were easily visible over the anterior surface of the upper third of the left chest. The lungs were normal to percussion and auscultation.

The cardiac apex impulse, which was forceful, heaving, and diffuse, was easily visible in the sixth intercostal space in the midaxillary line, 15 cm. from the midsternal line. There was a palpable pulsation in the third right intercostal space, approximately 6 cm. from the midline. On percussion, the heart was thought to be greatly enlarged to the left, and an area of parasternal dullness 9 cm. wide was found at the level of the first interspace. The arch of the aorta was slightly above the suprasternal notch and presented itself as a firm, pulsating, globular mass. A soft systolic thrill was felt over the cardiac apex, and a loud, harsh, rasping systolic murmur

was audible over the same area. An inconstant soft, blowing, systolic murmur could be heard over the base of the heart. No diastolic murmurs were present. The cardiac mechanism was normal except for numerous extrasystoles. The pulse at the right wrist was barely perceptible and so weak that estimation of its rate was impossible. The left radial pulse was 94 per minute, strong, and of good volume. The blood pressure in the right arm was 100/90 and in the left arm 190/100, both readings being obtained with the patient lying supine in bed. The vessels in all four extremities presented a diffuse sclerosis of the Mönckeberg variety.

Abdominal, pelvic, and rectal examinations were essentially negative.

The cranial nerves were intact except for right-sided facial hemiparesis and lingual deviation to the left. The deep reflexes were slightly hyperactive on the left, the abdominal reflexes depressed on the right, and plantar reversal signs were not obtained. Motor power was completely gone in the right upper and lower extremities and the right side of the face.

The clinical impression at this time was that the patient had suffered a cerebrovascular accident on the left side, due to thrombosis, with resultant right-sided hemiplegia and facial weakness. To this were added the diagnoses of aortic dilatation with aneurysm of the arch and compression of the innominate and left common carotid arteries, and left-sided torticollis.

A note made in the clinical record on February 4 described the patient as able to respond at times and as having persistent right-sided flaccid hemiplegia and facial paralysis. Positive Oppenheim and Chaddock signs were obtained for the first time, but the Babinski response remained flexor in type bilaterally. The left radial pulse was full and the blood pressure in the left arm was recorded as 200/100. The right radial pulse was still imperceptible and the blood pressure reading in this arm was noted as 90/85. The other signs remained unchanged.

Laboratory Reports.—Urine and stool examinations were negative on several occasions. Blood studies on admission showed that the hemoglobin was 15.6 grams, the erythrocyte count 5,700,000, and the leucocyte count 15,650, with 80 per cent neutrophiles, 11 per cent lymphocytes, and 9 per cent monocytes. Blood chemical analyses two days after admission showed a urea of 42 mg. per cent and carbon dioxide combining power of 32 volumes per cent. The blood Kahn reaction was one plus. Clear spinal fluid released under an initial pressure of 15 cm. of water contained three cells, all lymphocytes, per c.mm. and gave a negative Pandy test. The spinal fluid Wassermann and Meinicke reactions and gold curve were all negative. Electrocardiographic tracings made on the patient's second hospital day indicated mild myocardial damage. Fluoroscopic and radiographic examination on the same day showed moderate enlargement of the heart to the left and a fusiform widening of the superior mediastinum, with displacement of the trachea to the left. This superior mediastinal mass was seen to pulsate under the fluoroscope and was thought to be a large aneurysm of the ascending aorta, with some involvement of the innominate artery. The lung fields were clear.

During her short stay in the hospital the patient was treated with supportive measures, but gradually became unresponsive, sank into a deep stupor, and died on Feb. 6, 1938, three days after admission and five days after the onset of her illness.

Necropsy.—Superficial examination of the body was essentially negative except for the left-sided torticollis deformity. On removing the breast plate there was encountered a globular mass, approximately 7.5 by 8 by 8 cm. in diameter, projecting anteriorly and upward from the superior portion of the anterior mediastinum. This mass was of unusual firmness, saccular in shape, and occupied all available space between the origin of the left common carotid artery and the first portion of the transverse aortic arch. Examination of the aneurysmal sac through a small window made in its anterior surface showed the lumen to be completely filled with an organized, laminated, ante-mortem thrombus. The left common carotid artery

at its origin was completely occluded by what appeared to be a cicatricial mass centering about the carotid ostium, and sealing together the intimal coverings in the first centimeter of its course. Immediately above its origin the left common carotid artery presented its usual size and possessed normal elasticity. It was impossible to determine definitely in the gross whether the occlusion was due to cicatricial stenosis caused by inflammation, compression by the aneurysmal mass, or both. Furthermore, it was impossible to identify the origin of the innominate artery; the only remnant of it was a small obliterated tubular structure coursing along the upper right side of the posterior surface of the aneurysm. The bifurcation of the innominate artery into the right common carotid and subclavian arteries, however, could be identified near this area, and the course of the innominate vessel traced toward the heart over the posterior surface of the aneurysm for a distance of 3.5 cm. Beyond this point the innominate artery, after coursing a distance of 0.5 cm. as an

Fig. 1.—Aneurysm of the arch of the aorta, showing occlusion of the ostium of the left common carotid artery (Case 1).

obliterated tubule, was lost in the posterior wall of the aneurysmal mass. Arising from the anterior inferior wall of the terminal portion of the transverse aortic arch was another smaller, shallow, saucer-shaped aneurysm, 3 cm. in diameter and 1 cm. deep. Within the ascending and transverse segments of the arch of the aorta the intimal surface was almost entirely occupied by puckered, pearly-white scars and atheromatous plaques.

The heart was moderately enlarged, flabby, weighed 500 gm., and was pushed to the left and backward by the aneurysm. The valve leaflets were all competent, and the mural endocardium was smooth and glistening.

The trachea and esophagus were patent and showed no evidences of compression or erosion.

The kidneys were remarkable only for moderate arterial and arteriolar nephrosclerosis.

The pia-arachnoid over the convexity of the cerebral hemispheres of the brain, which weighed 1075 gm., showed patchy areas of milky opacity which were interpreted as the result of chronic leptomeningitis. The cerebral veins were congested and numerous atherosclerotic rings were seen in the vessels of the arterial circle of Willis. The left internal carotid and left middle cerebral arteries at their point of juncture with the arterial circle were completely occluded by an ante-mortem thrombus which extended for a distance of 3 cm. into the latter vessel. Microscopic examination of numerous sections of both vessels at their point of anastomosis with the arterial ring and at regular intervals along the first 2 cm. of their courses disclosed that their lumina were completely filled with a recent thrombus composed of corallike laminae of platelets with marginal leucocytes and intervening red corpuscles and fibrin. The intimal layers in all sections

Fig. 2.—Posterior view of the same specimen as in Fig. 1, showing occlusion of the innominate artery.

were markedly thickened and showed extensive atheroma, and also miliary erosions of the endothelial lining, covered by thrombi, and hyalinization of the new connective tissue which bulged from the arterial walls for some distance into their occluded lumina. Horizontal section through the brain at the level of the basal nuclei revealed a recent, massive, wedge-shaped area of infarction replacing the greater portion of the left temporal lobe, involving the anterior left caudate nucleus, the internal capsule in its entirety, the lenticular nucleus, thalamus, and island of Reil, extending posteriorly to involve the anterior extremities of the optic tract. Even with definite microscopic proof of the existence of an ante-

mortem thrombus in the internal carotid and middle cerebral arteries it is difficult, if not impossible, to explain with certainty the origin of the occluding clot. From the data at hand, however, two feasible explanations can be offered. The occlusion could have occurred because of: (1) embolus originating in the aneurysmal thrombus and passing by way of the left subclavian and vertebral arteries to the point of occlusion; or (2) thrombosis of the middle cerebral artery resulting from intimal damage due to arteriosclerosis. However, it would seem very unlikely that an embolus would seek out such a circuitous pathway as is described by the right-angled origin and spiral course of the left vertebral artery. This improbability and the lack of embolic phenomena in the remaining viscera would tend to support the second possibility.

Histopathology.—The histologic examination of the aortic arch and its major vessels was carried out on sections stained by (a) hematoxylin and eosin, (b) hematoxylin and Van Gieson, and (c) Levaditi's stain. Transverse sections through the arch of the aorta and the innominate and left common carotid arteries at their points of occlusion showed marked intimal proliferation, hyalinization, ulceration, and necrosis, overlying a distorted, scarred media dotted with localized areas of necrosis and cellular infiltrate composed for the most part of numerous lymphocytes, plasma cells, and foreign-body giant cells. In several places these cellular accumulations assumed the form of miliary gummas. Similar, smaller, but well-defined, areas of necrosis and lymphocytic infiltration were seen in the adventitial coats of all the occluded vessels, the cellular elements being arranged in the form of perivascular lymphocytic "collars" about the vasa vasorum. The whole of the intimal bundle in all sections stained a definite pink with Van Gieson's stain. Levaditi preparations failed to reveal any spirochetes.

CASE 2.—*History:* M. M., 33 years of age, a colored woman, was brought to the receiving ward of the Cincinnati General Hospital, Sept. 30, 1933, shortly after being discovered unconscious on the street. According to the history obtained from a daughter, the patient had suffered a "stroke" with resultant right-sided hemiplegia and complete aphasia three and one-half years prior to her present accident. In the interim she had regained some use of her right arm and leg, could say a few words, and apparently was enjoying fair health except for numerous fainting spells. These latter seizures were described as periods of complete unconsciousness during which the patient appeared to be lifeless except for respirations. She had received a small amount of antisyphilitic treatment before admission. The patient had lost 40 pounds during the preceding two years. The hospital course was uneventful except for three or four attacks of syncope and weakness brought on by sitting upright and relieved by lying down. Approximately two months after admission the patient suddenly sat up in bed, expectorated three ounces of blood, and twenty minutes later died.

Examination.—The patient was a well-developed colored woman apparently comfortable in bed while lying down. The skin over the shoulder girdle, upper extremities, head, and neck was less warm than over the rest of the body. The lips and nail beds were cyanotic. The right pupil was slightly larger than the left, but both reacted well to light and in accommodation. Examination of the neck showed diffuse enlargement of the thyroid gland, deviation of the trachea to the right, no tracheal tug, and absent pulsations in both carotid arteries. Except for slight lifting of the upper sternum with each heart beat the chest was essentially negative. Paramanubrial dullness was present on both sides in the first and second intercostal spaces. The cardiac apex was visible in the fifth left intercostal space 11 cm. from the midsternal line. No murmurs could be heard, the aortic second sound was louder than the pulmonic second, and the heart sounds were of "tic-tac" quality. No pulse could be felt in either upper extremity and the blood pressure could not be measured in the arms. In the lower extremities a systolic pressure of 120 was noted on several

occasions. Dorsalis pedis pulsations were present bilaterally. Pelvic examination revealed a large fibroma of the uterus. The arms and hands on both sides were definitely atrophic.

Laboratory Reports.—Examination of the urine and stools yielded negative results on all occasions. The blood showed a hemoglobin content of 80 per cent, an erythrocyte count of 5,400,000, and a leucocyte count of 7,500, with a normal blood smear. The blood Wassermann reaction was strongly positive. The spinal fluid showed a trace of globulin and three cells per c.mm. The spinal fluid Wassermann reaction was positive and the gold curve was reported as 0013443211. The basal metabolic rate was minus 6 per cent. The roentgenologist reported marked prominence of the aortic knob and thickened pleura over the right apex.

Necropsy.—The body was that of a well-developed, moderately obese colored woman of middle age. On removing the heart a firm mass, 5 by 5 cm. in diameter, was encountered in the upper mediastinum, which was identified as a saccular outpouching of the transverse arch of the aorta, filled with a laminated blood clot. The aortic intima in this region showed scattered, elevated, tough, pearly-white plaques edged with a thin rim of scar tissue.

Glove-finger projections of the ante-mortem thrombus situated in the aneurysm extended into and completely occluded the innominate, left common carotid, and left subclavian arteries. The vessels distal to the aneurysm showed no noteworthy change. There was no ulceration by the aneurysm into the esophagus or trachea. The remaining macroscopic findings were not significant except for caseous pneumonia, purulent bronchitis, and focal areas of cerebral encephalomalacia.

Histopathology.—Microscopic examination of representative sections of the aorta showed fibrous thickening of the intimal lining, with fragmentation and lymphocytic infiltration of the media. The vasa vasorum of the adventitia presented the usual perivascular lymphocytic "collars" seen in syphilitic aortitis.

DISCUSSION

In view of the complete occlusion of the large arterial trunks which carry blood to the head, neck, and arms, it would have been interesting to have traced out the possible channels of collateral circulation. However, such detailed dissection of the anastomoses in the neck and arms would have necessitated special autopsy permission which unfortunately was not obtained in the two cases here reported.

It is interesting to note that in all of the five previously reported cases the diagnosis of syphilis could be made either on the basis of post-mortem findings or serologic tests. In Broadbent's case there was a positive history of syphilis and characteristic lesions were demonstrated in the aorta. In Crawford's and in Kampmeier and Neumann's cases the serologic tests were positive for syphilis and the diagnosis was said to have been verified roentgenologically. No serologic data were available in Shikhare's report, but a definite aneurysm was demonstrated post mortem. Both gross and microscopic evidences of syphilis were presented in the case reported by Cohen and Danie. Positive serologic tests and gross and microscopic lesions of syphilis occurred in both cases here reported.

Of further interest is the fact that the presenting complaint in all cases, both those reviewed and those here reported, was referable to the cerebrum, evidently caused by cerebral anoxemia.

In all cases presented there was complete absence of pulsations in the carotid and radial vessels, with the exception that a weak carotid pulse was present on one side in Broadbent's patient and a radial pulse in the left arm in the first case reported here. Incidentally, it should be noted how, in this same patient, the collateral circulation reached such a degree of perfection that a blood pressure of 100/90 could be measured in the right arm, which was later shown, anatomically, to be completely without any main arterial supply.

SUMMARY

Two cases of aneurysm of the aortic arch with absent carotid and radial pulses are reported. In a review of the literature but five similar cases were found, in only three of which was there a post-mortem examination. Syphilis was undoubtedly present in all of these cases. The clinical picture in all of the cases was that of cerebral disease, with attacks of dizziness and syncope, together with absent pulsations in the superficial vessels of the neck and upper extremities.

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ELECTROCARDIOGRAPHIC CHANGES INDUCED BY THE TAKING OF FOOD

A Preliminary Report

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ALTHOUGH Wilson and Finch[1] reported certain transient changes following the ingestion of ice water, there are, as far as we have been able to ascertain, no reports in the literature concerning the effect on the electrocardiogram of taking food. An investigation of this matter was undertaken by us, early in 1938, with the object of determining whether or not ordinary meals induce changes of sufficient magnitude to be taken into consideration in the clinical interpretation of electrocardiograms.

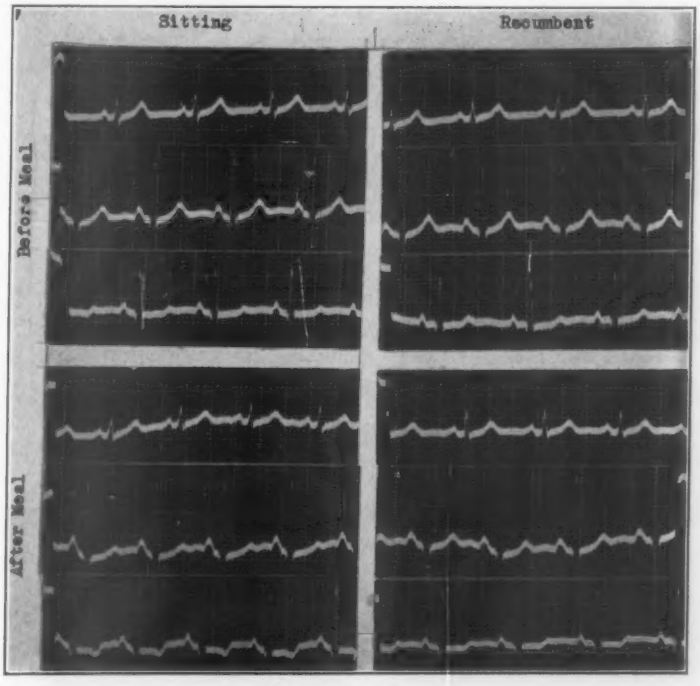

Fig. 1.

Electrocardiograms were made on nine normal, healthy, young adults before, and again within thirty minutes following, an ordinary mixed meal. Of these, seven showed changes which are of some in-

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Received for publication Dec. 10, 1938.

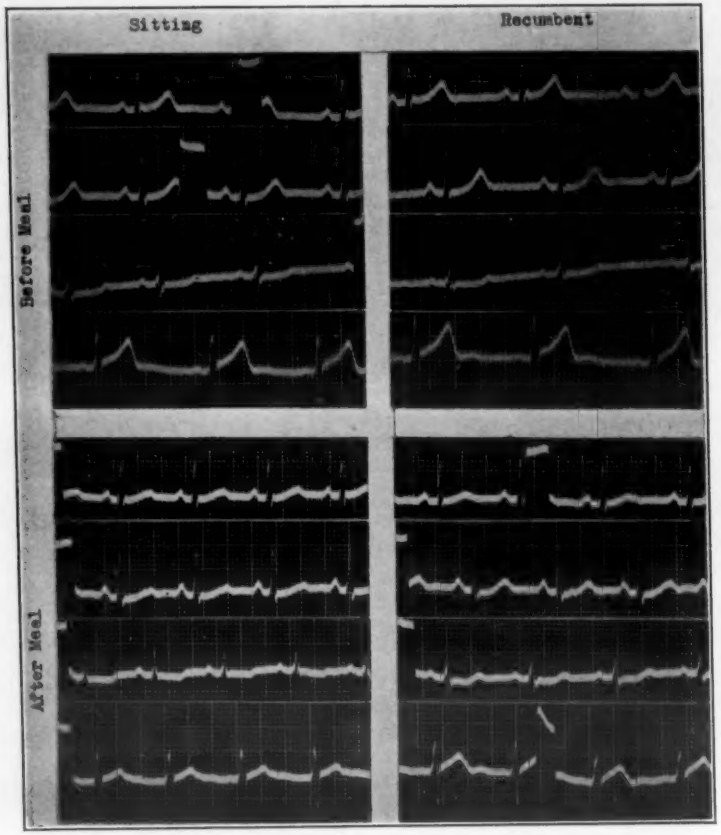
Sitting
Recumbent
Before Meal
After Meal

Fig. 2.

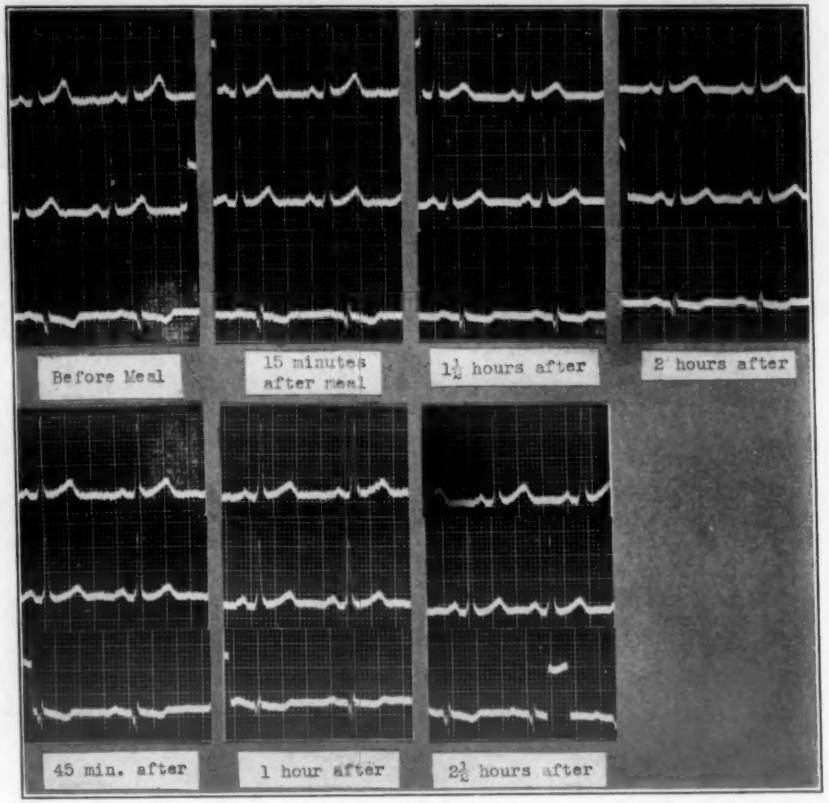
Before Meal
15 minutes after meal
1½ hours after
2 hours after
45 min. after
1 hour after
2½ hours after

Fig. 3.

terest. These changes consist of a 30 to 50 per cent decrease in the height of the T-waves in Lead I or III, or in all three leads. In one case (Fig. 1), T_3, which was previously upright, became inverted. In another (Fig. 2), T_1 not only was markedly lowered, but became notched also.

Thus far the cause of these changes has not been determined. They cannot be correlated with change in heart rate, for in one case the rate remained the same. Again, the change in the T-wave is not proportionate to the degree of rate change in any case. In no case did sufficient change in the electrical axis occur to explain the alterations in the height of the T-waves.

Several subjects have been studied in an attempt to discover the time of onset, and duration, of these changes. It has been found that the change does not reach its maximum until about one hour after the food is taken. It persists at this level for one and one-half to two hours, and then begins to disappear (Fig. 3).

CONCLUSION

Though no final conclusion is possible at the present time, it seemed justifiable to render a preliminary report of the finding of certain changes in the electrocardiogram, following the taking of food, in seven of nine normal individuals, together with the behavior of these changes with respect to onset and duration in several other (also normal) individuals.

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Department of Clinical Reports

PRIMARY TUMOR OF THE HEART (ENTRANCE OF THE PULMONARY ARTERY)*

Case Report

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PRIMARY tumors of the heart are of sufficient rarity to merit report. The present instance concerns a woman, 46 years of age, who entered St. Mary's Hospital in obvious, severe, congestive heart failure, and died within thirty hours. Fortunately, there was time to observe her and to record some important data. There was a negative history of anything betokening rheumatic fever or its equivalent. There was no hypertension. While somewhat frail, she had never been conspicuously ill. She had had three children, with normal deliveries, the youngest of whom was 17 years old.

She had consulted her doctor about an upper respiratory infection early in October, 1937. During the succeeding winter she had lost six pounds, which reduced her weight to 102 pounds. She had noted increasing fatigue and dyspnea on slight exertion, but she had had no orthopnea. In March, 1938, her physician diagnosed hypochromic, microcytic anemia, and gave her extra vitamins and iron. A month later her hemoglobin was recorded as 43 per cent, and she felt no better. In keeping with this type of anemia, she had decidedly brittle and scaphoid finger nails, a smooth tongue, and a very indifferent appetite. A systolic murmur was heard at the base of the heart. Edema noticeable to the patient first appeared in the third week of May, 1938, and thereafter her discomfort and incapacity increased rapidly. There was conspicuous absence of precordial pain, and nothing comparable to angina of effort. A few days before entering the hospital there had been some sense of oppression and fullness in the abdomen. The dark color of the stools was thought to be a result of the iron medication, and this proved to be correct.

On the day of admission to the hospital her breathing was hurried, even, and nonstertorous, at a rate of about 36 per minute. There was a dusky pallor, lending a suggestion of the "café au lait" appearance. This, coupled with a very loud systolic murmur heard over the precordium and a history of severe anemia, led to a careful search for petechiae. None could be found, nor could the spleen be palpated. It was noted that she had extreme changes in the nails (koilonychia, brittleness), and that the tongue was smooth and showed some atrophy of the papillae, without actual glossitis. The liver was very easily palpable, and was down well below the costal margin. The neck veins were greatly distended, so much so that pressure upon the liver did not distend them any more. Unfortunately, we did not have the opportunity to measure the venous pressure; and in her semiconscious state we could not estimate the arm-to-tongue circulation time. The abdomen had a somewhat doughy feel, indicating some ascites. Over the base of the right lung the percussion note was dull to flat, and bronchial breathing and whispered pectoriloquy were present in this area. The apex thrust of the heart was out somewhat to the left. The blood pressure at that time was somewhat low (about 100/70). The eye grounds were entirely negative.

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Received for publication Nov. 4, 1938.

Differential Diagnosis.—The patient was suffering from congestive heart failure of high degree, from which she died very shortly, while an attempt was being made, by means of slow intravenous injection, to combat the acidosis which the carbon-dioxide combining power of 30 volumes per cent indicated.

With edema, some ascites, hepatic enlargement, evidence of fluid in the right pleural cavity, and low voltage in all leads of the electrocardiogram (she did have considerable fluid in the pericardial sac), was she in the *terminal stage* of congestive heart failure, with subacute bacterial endocarditis superimposed upon either an old rheumatic or congenital defect? With the type of anemia present, and the characteristic changes in the nails and tongue, one could be quite sure that this anemia was not secondary to subacute endocarditis. Examination of the blood just before death showed that the hemoglobin was 75 per cent, the erythrocyte count 4,900,000, the leucocyte count 13,800, and the differential count normal. These high counts imply hemoconcentration through dehydration and acidosis.

The loud basal systolic murmur raised the question of mitral valve involvement and indicated caution about attaching too much importance to anemia as a possible factor. The definite liver enlargement and the great engorgement of the veins of the neck indicated tricuspid regurgitation with right ventricular decompensation. The bedside roentgenogram gave confirmation of cardiac enlargement both to the left and right. The absence of any thrill, clubbing of the fingers, and history of cyanosis spoke against pulmonary stenosis of long duration. Further comment will be made later upon some of these items.

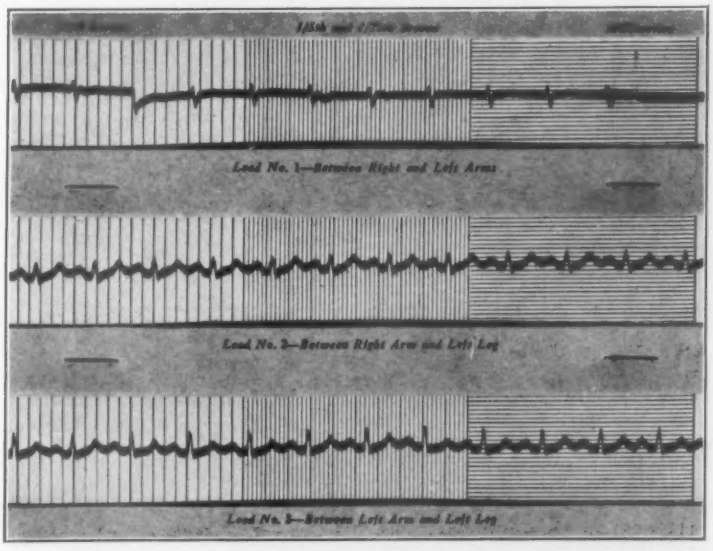

Fig. 1.—Electrocardiogram taken a few hours before the patient died. Low voltage and right axis deviation are noted. Isoelectric T in Lead I.

Dr. George L. Berdez, pathologist at St. Mary's Hospital, reported that on removing the sternum it was obvious that a very unusual condition obtained. The following is excerpted from Dr. Berdez' extensive and detailed protocol:

"Cardiac dilatation more to the right than to the left, with resultant extreme dilatation of the right ventricle. The aorta and the aortic valves were normal. On opening the right ventricle a polypoid tumor projected through the pulmonary orifice, producing at once high grade stenosis and moderate insufficiency. The growth was about 2½ cm. in diameter. It had a grayish-white color, and varied from a

compact structure in some areas, to a softer and edematous consistency. Upon opening the pulmonary artery itself this whitish tumor was seen to actually involve the pulmonary valve, and to spread to the adjacent endocardium for a distance of about 2½ cm. Sectioning the wall of the pulmonary artery, the tumor tissue was seen to invade its whole thickness, without, however, perforating it. The pulmonary valve invasion had rendered the cusps somewhat softened, thickened, to a thickness of 0.3 cm., or more. The tumor spread along the course of the pulmonary artery, to the right and to the left pulmonary arteries, and to the beginning of their main branches. The lumen of the right pulmonary artery was somewhat narrowed; those of the main branches of the left pulmonary artery were slightly dilated; the wall of these latter branches appeared somewhat thin, and the surface demonstrated faint longitudinal striae. No emboli were found. There was moderate emphysema of the left lung, but little else was demonstrated.

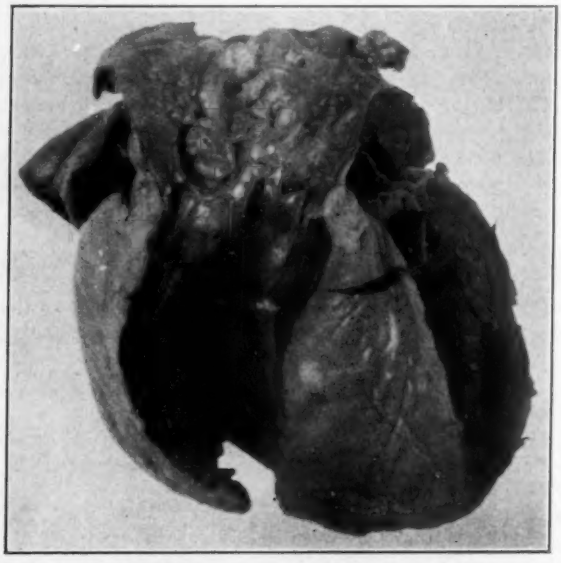

Fig. 2.—The heart is shown with the right ventricle opened. The diffuse tumor rises from the background of the opened pulmonary artery.

"Microscopically, the tumor cells were decisively polymorphous (irregular in size and shape); in places the cells were spindled, at others rounded. The cell nuclei were also irregular in shape and size (elongated, rounded, irregular), and were moderately rich in chromatin. Some of the nuclei were hypochromatic. Only a few showed mitoses. The development of a relatively few fibrillar cellular elements in some places accounted for the edematous areas; areas of connective tissue and fibrosis accounted for the firmer zones. The tumor cells invaded deeply into the wall of the artery, as was intimated in the growth. There was shown an occasional area of necrosis, with numerous Pmn's (polymorphonuclear leucocytes) associated. The adventitia of the pulmonary artery was edematous, and showed areas of lymphatic infiltration. Sections of the right pulmonary artery showed the tumor invading the intima, and the resultant thickening accounted for the tendency to stenosis. It was likely that the thinning out of the left pulmonary artery followed the insufficiency of the pulmonary valve. No metastases were found."

The final diagnosis was neoplastic stenosis, grade III, of the pulmonary valve, with grade I insufficiency of the pulmonary valve; and marked hypertrophy and dilatation of the heart. The tumor proved to be a polymorphous cell sarcoma, with a very limited amount of fibrosis.

Fig. 3.

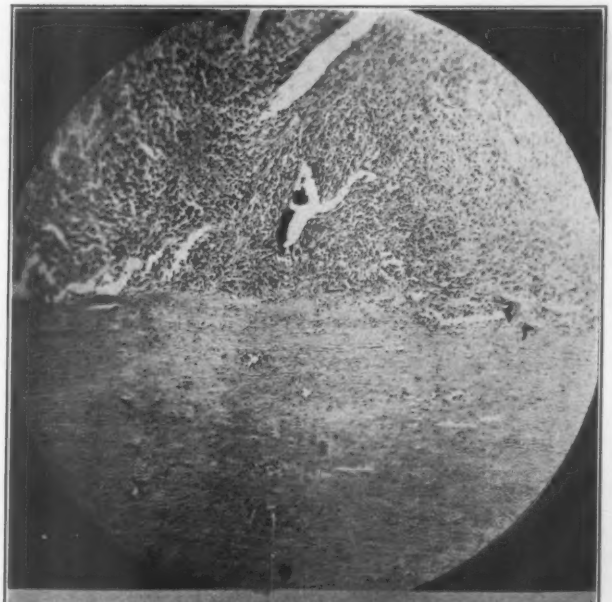

Fig. 4.

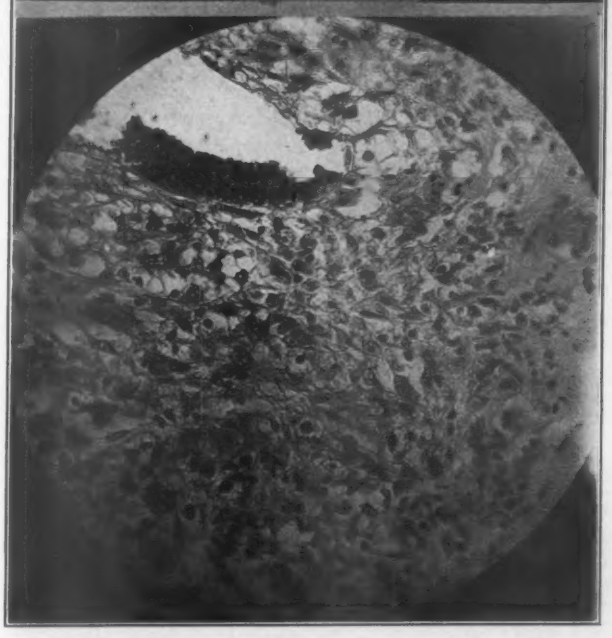

Fig. 3.—A low-power microscopic section of the tumor invading the adjacent wall of the pulmonary artery.

Fig. 4.—High-power microscopical section of the tumor, showing the polymorphous cellular pattern.

DISCUSSION

Strouse[1] has recently reported a case with a complete bibliography of primary tumors of the heart. For that reason we shall limit our references. His case report concerns a man who had symptoms of heart disease for forty-three years. The tumor, in keeping with the protracted history, was a benign myxoma of the right auricle. Strouse refers to the articles by Yater,[2] who gave a review of the literature in 1931, and Mead,[3] who reported upon metastatic invasion from lung carcinoma in 1932. The general incidence of primary tumor of the heart is estimated at only 0.03 per cent, whereas metastatic growths give an incidence of 0.5 per cent. Since primary malignant tumors of the lungs or mediastinum may readily reach the heart, either through lymphatic drainage and venous return or by direct extension, it is not strange that most of such growths occur in the right side of the heart and, usually, the right auricle. The primary source might, however, be any portion of the body, with the possible exception of the brain, whence malignant tumors rarely metastasize. Few of these cardiac metastases produce symptoms; and if they do they are obscured by an excess of disturbances due to the primary growth. It is theoretically possible that both primary and secondary tumors may invade the conducting mechanism, or begin in the epicardium or pericardium and produce the signs (including the electrocardiographic) of pericarditis. Barnes, Beaver, and Snell,[4] in 1934, reported the first case in which a primary malignant tumor was diagnosed ante mortem. They had the advantage of a deltoid muscle biopsy from an area of tenderness. This, coupled with the electrocardiographic proof of atrioventricular dissociation occurring acutely, led to the presumptive and correct diagnosis of a cardiac tumor. In Shelburne's case,[5] reported in 1935, the correct diagnosis was likewise made ante mortem from pericardial evidence of a primary sarcoma of the pericardium, with electrocardiographic localization. Willius[6] reported a fibrosarcoma of the right auricle in May, 1938. He gives a reference to Perlstein,[7] who reported on sarcoma of the heart in 1918 and collected thirty cases of primary tumor, adding one of his own. Willius brings up the question of future possibilities of ante-mortem diagnosis and discusses certain electrocardiographic aids. Epicardial invasion, irritation, or fibrin accumulation, usually in association with pericarditis with effusion, yields reliable electrocardiographic diagnostic hints.

Boman[8] has recently reported upon a primary sarcoma of the pericardium undiagnosed before death. He found Yater's classification of clinical types and their symptoms useful. Obviously, the pericardial irritation, fluid accumulation, and tendency to cardiac tamponade are more likely to induce obtrusive symptoms and physical signs than intramuscular or intracardiac protrusions.

Concerning the problem of making ante-mortem diagnoses of primary cardiac tumors, Strouse[1] makes the following logical comments: "It

must be admitted that practically all the information so far published has been based on ex post facto reasoning." However, this is the manner in which practically all improvements in diagnostic ability have been made. In retrospect, in our case, we feel that there was evidence sufficient, if it had been correlated, to at least lead to a presumptive diagnosis. Conditions that arise so rarely are likely to be totally out of mind. The following circumstances stand out conspicuously, and it may be worth while to group them in an attempt at summarizing such available data as might in later experience prove fruitful.

1. This patient did not have the usual history of any of the classical constitutional, congenital, or localizing cardiac lesions which commonly lead to congestive failure. Meroz,[9] in his clinical report of three cases of primary tumor of the heart, strongly emphasizes this feature.

2. Her collapse was rapid and came without any suggestion of previous left ventricular strain. It was her first attack of congestive failure.

3. The right-sided heart failure, with such extreme overfilling of the veins and massive engorgement of the liver, without obvious, protracted ascites, dominated the picture. (Reference has already been made to the failure to secure the arm-to-tongue circulation time and a measurement of the venous pressure.) Acute cor pulmonale existed.

4. The lowering of the carbon-dioxide combining power of the plasma and the accompanying hyperpnea portray the compensatory efforts of the body to maintain homeostasis, or equilibrium.

5. Despite the evident need of oxygen she was not cyanotic, but had that murky hue which has been called "café au lait." She was not anemic enough to make visible cyanosis impossible on Lundsgaard's quantitative basis. Although there was an abundance of blood in the venous system, well oxygenated in the lungs, it was nevertheless unable to reach the systemic capillaries.

6. Had this tumor been of long duration, and had there been recurring attacks of congestive failure (see Strouse's report[1]), the right ventricle should have been markedly hypertrophied. In that sense it might be well to consider right-sided heart obstruction as a whole. Blood fails to empty from the great veins into the right auricle in constrictive pericarditis. We have seen a large, metastatic, carcinomatous, fibrin-mixed plug grow into the mouth of the superior vena cava, gradually impeding flow from the inferior cava, as well. Theoretically, the tricuspid orifice could be blocked, but as an isolated phenomenon this does not occur. Blockage within the pulmonary arterial system (Ayerza's disease, pulmonary sclerosis and hypertension, etc.) produces prolongation of the circulation time, but the acute venous overfilling, as seen here, is not a feature.

The electrocardiogram, although it shows right axis deviation, does not indicate marked right ventricular preponderance. If there was a tumor plugging the right ventricular exit, and the heart was unable to accept

blood from the overfilled pulmonary veins, and if the evidence by ordinary physical methods, roentgenographic examination, and electrocardiographic tracings spoke against actual hypertrophy or thickening of the right ventricular wall, then it would logically be deduced that the tumor must be rapidly growing, and hence malignant.

7. The murmur at the base deserves analysis. With our patient's type of anemia, one of us (W. C. M.) felt that such a systolic murmur was neither uncommon nor determinative. In retrospect, however, the type of murmur, with increased venous pressure, and without any thrill, might well make one think of the possibility of pulmonary ostial obstruction that was of the diffuse, rather than the abrupt, type. This conclusion might be drawn from the fact that classical thrills are produced by obstructions which permit vibration and involve a limited opening, beyond which the stream enters an open space. This is exactly what did not obtain in this instance; therefore, a systolic murmur, without a thrill, occurring in a case of diffuse obstruction, might very well suggest that the stenosis is neoplastic in origin.

SUMMARY

We are reporting another instance of primary malignant tumor producing extreme diffuse stenosis of the pulmonary artery at its orifice. It was a polymorphous cell sarcoma. It invaded the wall of the pulmonary artery to, and beyond, its right and left branches. We have made brief reference to some of the available literature and have discussed some of the symptomatology and physical findings. Such an analysis may be of some assistance in the attempt to make antemortem diagnoses of this disease.

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VENTRICULAR FIBRILLATION AS A CAUSE OF SUDDEN DEATH IN CORONARY ARTERY THROMBOSIS*

Report of a Case

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THE dramatic occurrence of sudden death has been of intense interest for centuries. Post-mortem examinations, by different investigators, of persons dying suddenly and unexpectedly, have shown a large preponderance of cardiovascular lesions. In Hamman's[1] series, such abnormalities were present in 91 per cent; and of sudden deaths from heart failure, 65 per cent were due to affections of the coronary arteries. It is well known that in patients with coronary artery sclerosis sudden death may occur in those who have, or those who have not, had an actual occlusion and that in the cases of nonocclusion it is more frequent in patients who have had anginal pain. Levy[2] has shown, in an analysis of cases of sudden death from coronary disease, in 1933, that the occurrence of coronary thrombosis in patients with coronary artery sclerosis triples the probability of sudden death. In our own series of coronary thrombosis cases, of 80 patients known to be dead, twenty were reported to have died suddenly.

The cause of this abrupt termination of life in coronary artery thrombosis is rarely cardiac rupture. This lesion was present in only three of 762 autopsy cases of coronary artery disease in Levy's[2] series at the Presbyterian Hospital in New York City. The sudden fatality in the great majority of these patients with coronary artery disease is due to abrupt cessation of the heartbeat—ventricular asystole. Allbutt's[3] theory of an overwhelming, sudden vagus stimulation, with paralysis of the pacemakers, causing cardiac standstill, has very little backing at the present time. The presumption exists that this sudden, unexpected death, both in patients with angina pectoris and those with coronary artery occlusion, is due to fibrillation of the ventricles. This presumption has developed in medical literature since Hoffa and Ludwig[4] demonstrated, in 1850, that electrical stimulation of the mammalian heart led to ventricular fibrillation and death. In 1888, McWilliam[5] propounded the theory of sudden death by ventricular fibrillation, a previously unrecognized form of failure of the heart's action in man. This view was fundamentally different from those entertained up to that time.

The strengthening of the opinion that ventricular fibrillation is the most frequent cause of sudden death in coronary artery disease rests chiefly upon a large amount of experimental and clinical data.

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Received for publication Dec. 1, 1938.

Ventricular fibrillation has been produced experimentally in the hearts of mammals by means of various electrical, thermal, mechanical, or chemical stimuli, or by the ligation of a main branch of a coronary artery. The arrhythmia outlasts the stimulation, and usually persists until the heart dies.

A striking similarity has been noted between the groups of symptoms associated with sudden death in patients with coronary disease and those attendant on ventricular fibrillation experimentally induced in animals.[5, 6] Observers have noted in both instances the abrupt loss of consciousness, disappearance of the pulse, fall of blood pressure to zero, muscular relaxation occasionally preceded by brief rigidity or convulsive movements, congestion of the neck veins, pallor, cyanosis, a few deep or gasping respirations, dilatation of the pupils, followed by death of the animal or patient.

Lewis[7] states that all forms of disordered heart action produced experimentally are known to occur clinically; and the reason that so few instances of ventricular fibrillation have been recorded in man is that the arrhythmia is, in all but the briefest instances, incompatible with life.

However, the recording of ventricular fibrillation in man has now been accomplished in numbers of instances, the great majority in persons whose death was expected and in whom the irregularity was recorded as a terminal development in the dying heart.[8-15]

Many examples of brief, transitory episodes of ventricular fibrillation have been recorded, as in the stage of ventricular standstill of Stokes-Adams seizures,[16-23] in the course of treating auricular fibrillation[16, 24] with quinidin, or following carotid sinus pressure in a patient with auricular fibrillation.[26] Dock[26] has stated that in man ventricular fibrillation establishes and maintains itself with difficulty.

Both von Hoesslin[13] and Penati[27] have recorded instances of ventricular fibrillation resulting in the sudden death of patients suffering from cardiac failure due to rheumatic heart disease; in both cases death followed an intravenous injection of strophanthin.

Published instances, however, of electrocardiographically recorded ventricular fibrillation causing sudden death in patients with known coronary disease are very few in number.

Hamilton and Robertson,[28] in 1933, obtained an electrocardiogram showing ventricular fibrillation in a patient during a fatal attack of angina pectoris. Autopsy showed sclerosis of both coronary arteries, but no occlusion or myocardial infarction. Meyer[29] took an electrocardiogram during a fatal attack of ventricular fibrillation in a patient who had previously had bundle branch block and evidence of myocardial disease. Calandre and Martin-Rodriguez,[30] and also M. Vela,[31] secured an electrocardiogram showing ventricular fibrillation on a patient during a fatal attack of angina pectoris. No autopsy was done in either instance.

In order to add to the meager electrocardiographic data at the time of sudden cardiac death, we are reporting the following case, which is an instance of ventricular fibrillation and sudden death within the first few hours following coronary artery thrombosis. No other electrocardiographic record of ventricular fibrillation occurring during the period of active myocardial infarction following coronary artery thrombosis has been found in a review of the literature.

REPORT OF CASE

H. T. E., a man 40 years of age, a university instructor in an eastern city, had for three weeks been having frequent attacks of substernal pain on effort, accompanied by a numb sensation in his left arm. The attacks averaged about 5 to 10 minutes in duration and had been promptly relieved by nitroglycerine. He had been advised to drop his work and come to Detroit, where he had relatives, for a rest. On Dec. 14, 1937, at 7:00 A.M., he developed a continuous, heavy, substernal pain, which was not relieved by the usual dose of 1/150 grain of nitroglycerine. At 4:00 P.M., nine hours later, the pain continuing, he arrived at the hospital heart station, having just taken another tablet of nitroglycerine without relief. He was obviously ill. His face was pale and his forehead covered with beads of perspiration. The history quite clearly was that of coronary artery occlusion of nine hours' duration, and it was thought best to have him admitted to the hospital without taking time for physical examination, but since the electrocardiographic instrument was readily accessible, a tracing was made (Fig. 1).

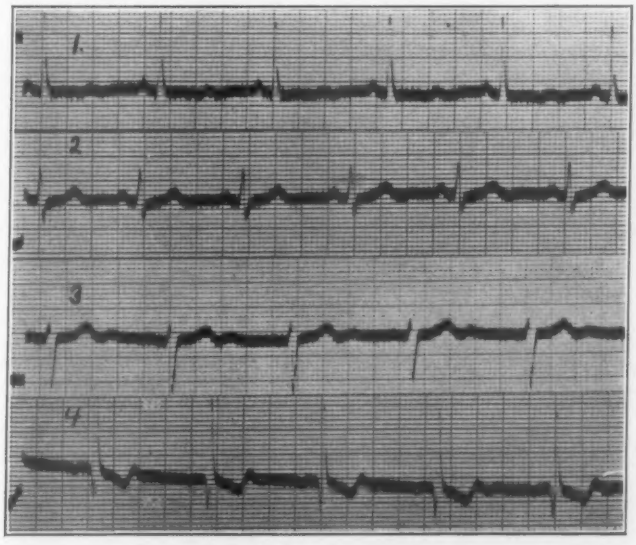

Fig. 1.—Electrocardiogram made nine hours after occlusion of the anterior descending branch of the left coronary artery, and five minutes before the development of ventricular fibrillation.

This electrocardiogram shows normal sinus rhythm, left ventricular preponderance, and diphasic T-waves in Lead I and Lead IV. Lead IV in this case was taken with the right arm electrode at the cardiac apex and the left arm electrode on the chest posteriorly.

As soon as this tracing had been completed the patient was given ¼ grain of morphine hypodermically. About three minutes later, while waiting for a wheel

chair to take him to his hospital room, he abruptly lost consciousness and gave a few irregular, clonic, convulsive movements. His pulse could not be palpated. Breathing was deep, irregular, and stertorous. The face was alternately pale, cyanotic, and congested. The pulsations in the neck were absent and the vessels became engorged. No heart sounds could be heard. The electrocardiographic electrodes were immediately reconnected, as soon as convulsive movements ceased, and while respiration was still occurring irregularly another electrocardiogram consisting of the standard three leads was recorded. At this time, very rapid, wide, diphasic oscillations of the string shadow were seen. During this recording respirations ceased except for an occasional gasp. The tracing taken at this time shows large, diphasic complexes of irregular height and frequency, occurring at a rate of 360, or more, per minute. The appearance of the tracing corresponds in every way to that of the previously published records of ventricular fibrillation in man and animals. In spite of the use of artificial respiration and the intracardiac injection of epinephrine, the patient was to all appearances dead following the completion of this tracing.

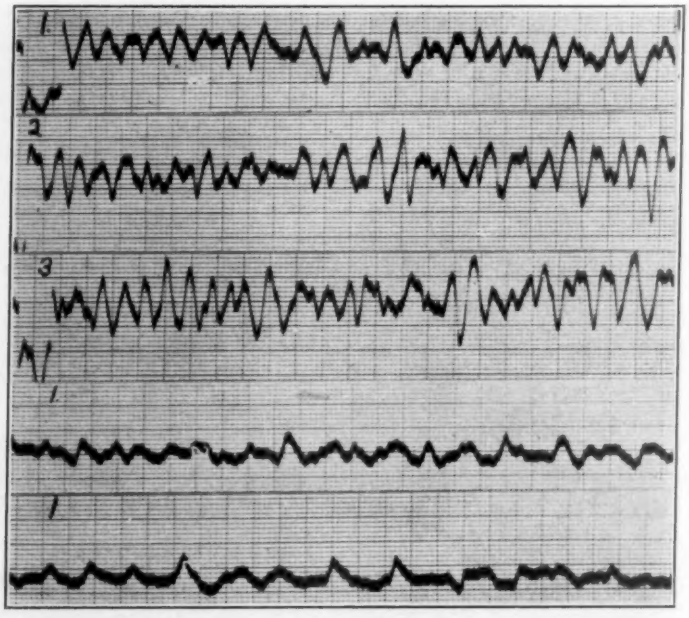

Fig. 2.—Electrocardiograms made immediately following a generalized convulsion. The first three tracings consist of the standard three leads and were made consecutively. The fourth and fifth are Lead I and were made at two-minute intervals.

About two minutes later another tracing was made from Lead I, and this was again repeated in two minutes (Fig. 2). Tracings were not continued beyond this point, so that we are not able to state how long the string movements continued. In the later tracings the amplitude of the oscillations was seen to be much smaller.

The autopsy was done by Dr. Penny. The cardiac findings alone were of interest. The myocardium of the left ventricle was softened over an area about 3.5 cm. in diameter, on the anterolateral surface, about 2.5 cm. above the tip. In this area, on section, the myocardium was mottled yellow in color. Elsewhere the myocardium of the left ventricle cut with increased resistance. Its wall averaged 1.3 cm. in thickness, and that of the right 0.7 cm. The coronary ostia

were patent, and the proximal aorta showed a few punctate atheromata. The anterior descending branch of the left coronary artery was extensively thickened and, in places, calcified from a point 1.5 cm. from the ostium to a point 3.0 cm. from the tip of the ventricle. At the proximal point of the thickening there was marked stenosis, and a small recent thrombus apparently completely occluded the lumen. The remainder of the artery was patent, but definitely stenosed and thickened. The left circumflex artery was also thickened and stenosed. The right coronary artery was dissected throughout and was markedly thickened by atheromatous plaques, but the lumen appeared adequate. The weight of the dissected heart was 390 grams.

Microscopic examination of the infarcted area in the left ventricle showed an early polymorphonuclear infiltration about the muscle fibers and slight haziness of their outlines, while a large amount of fibrosis was apparent in some areas (Fig. 3). Section through the thrombosed coronary artery showed marked thickening of the wall and an atheromatous node almost obliterating the vessel, leaving a tiny crescentic lumen to be plugged by the fresh thrombus.

Fig. 3.—Section through the thrombosed coronary artery, showing marked thickening of the wall and an atheromatous nodule almost obliterating the vessel, leaving a tiny crescentic lumen which was plugged by the fresh thrombus.

COMMENT

In this case ventricular fibrillation coincided with the sudden death of a patient who had had a thrombosis of the anterior descending branch of the left coronary artery and an early infarction of the anterior surface of the left ventricle. It is true that we were not fortunate enough

to record the transition from normal sinus rhythm to ventricular fibrillation, and hence are unable to state whether or not ventricular tachycardia or a period of cardiac standstill preceded this.

The first electrocardiogram, taken five minutes before death, deserves comment in that it showed no definite evidence of myocardial infarction, although, judging from the history, this had begun nine hours earlier, and autopsy disclosed that early infarctive alterations had definitely occurred. But, whereas with a sizable area of myocardial infarction characteristic electrocardiographic changes usually develop within the first few hours, it has occasionally happened that significant alterations did not appear until the following day.

In reviewing the treatment of the ventricular fibrillation in our patient and the other five with angina pectoris or coronary sclerosis it is apparent that it was entirely futile. In all but one patient adrenaline was injected into the heart, and, in two, cardiac massage was attempted.

The physiologists[32] and cardiac surgeons[33, 34] have made considerable strides in arresting experimentally produced ventricular fibrillation in animals by means of electric counter shock in combination with cardiac massage and the combined use of procaine hydrochloride, adrenaline, and calcium intravenously. Their work has been carried out, for the most part, on animals whose hearts were exposed by surgical incision.

The probability of being able to revive a patient with coronary occlusion from ventricular fibrillation by such means seems extremely remote.

SUMMARY

A case of coronary artery thrombosis is reported in which ventricular fibrillation, electrocardiographically recorded, caused sudden death.

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A SYNDROME OF EXOPHTHALMIC GOITER, ACUTE RHEUMATIC CARDITIS, AND HEART BLOCK*

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IN 1825, Parry[1] originally described a series of six cases of exophthalmic goiter. Rheumatic fever preceded the goitrous enlargement in one patient, and organic heart disease was present in two others. Basedow[2] (1840) described four cases of exophthalmic goiter; three of the patients had previously had rheumatic fever and valvular disease. Numerous reports have been made on the combination of exophthalmic goiter and rheumatic fever, notably, by Markham[3] (1858), Garnier[4] (1899), Froment[5] (1906), Bouchut[6] (1906), Coudray[7] (1909), McCarrison[8] (1917), Cabot[9] (1929), and others.

Chronic rheumatic valvular disease is considered an occasional complication in exophthalmic goiter by White[10] (1937). Yet Vincent[11] (1906) reported that of 156 cases of acute rheumatic fever, hyperthyroidism was a complication in 86. Conversely, Maher and Sittler[12] (1936) reported 180 cases of thyrotoxicosis, in 23.3 per cent of which rheumatic valvular involvement was present.

The occurrence of heart block and exophthalmic goiter has been reported frequently, among others, by Merklen[13] (1882), Lewis[14] (1913), Reilingh[15] (1915), Dameshek[16] (1924), Goodall and Rogers[17] (1927), Simon[18] (1927), Easton[19] (1930), Cameron and Hill[20] (1932), Wedd[21] (1932), Davis and Smith[22] (1933), Carey[23] (1934), Kremer and Laplace[24] (1936), and Steuer[25] (1936).

A review of these reports shows a variation in opinion regarding the relationship of the heart block and the hyperthyroidism. Certain authors have suggested that the hyperthyroidism caused the block, but in cases in which autopsies were performed organic inflammatory lesions usually were found.

The authors have observed a number of patients with typical exophthalmic goiter associated with acute carditis. Of this group, four whose records are complete will be reported in detail. The patients were observed during thyroidectomy and from six months to four years thereafter.

REPORT OF CASES

CASE 1.—E. S. was a 20-year-old, white, unmarried, shipping clerk. His family history was recorded as negative for goiter, rheumatism, and heart disease. As a child, he frequently developed sore throats, so that tonsillectomy and adenoidectomy were performed at 11 years of age. At 14 years of age, acute rheumatic fever developed. At 18, he was subjected to a resection of the nasal septum.

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Received for publication Dec. 7, 1938.

Examination of the patient in the Cook County Hospital revealed the typical findings of exophthalmic goiter, with a basal metabolic rate of plus 50 to plus 55 per cent. The cardiac findings were characteristic of mitral stenosis and insufficiency.

The first electrocardiogram showed a prolonged P-R interval with fusion of the P and T waves. Serial electrocardiograms taken during the following weeks showed various types of block, including Wenckebach periods, occasional dropped beats, 2:1 ratio, and complete auriculoventricular block. The temperature tended to be slightly elevated, ranging from 98° F. to 100° F., and there was a leucocytosis which did not exceed 14,200. He complained occasionally of sore throat and had a few nosebleeds. There was mild joint distress, but no objective manifestations of arthritis were present.

The administration of iodides was effective in lowering the basal metabolic rate to plus 17 per cent, and subtotal thyroidectomy was accomplished without incident.

Examination three weeks after operation showed no change in the murmurs, and no difference in the size and shape of the heart roentgenographically; the electrocardiogram showed a normal P-R interval. The basal metabolic rate was normal. The patient returned to work and three years later showed no evidence of hyperthyroidism, but the same valvular defects persisted.

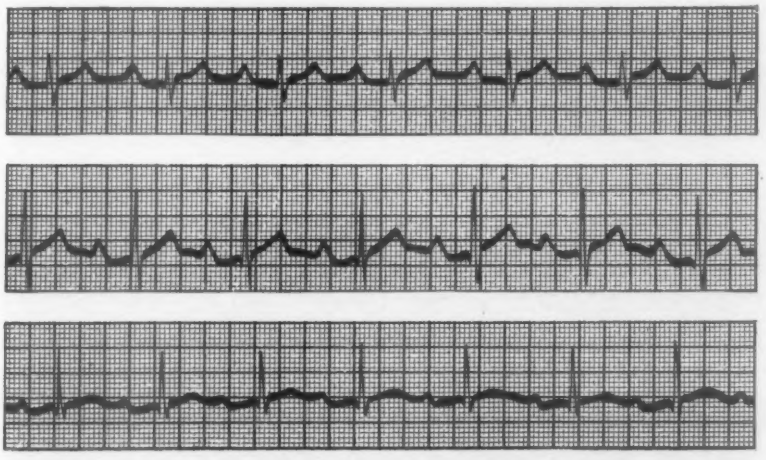

Fig. 1.—Electrocardiogram in Case 1 (E. S.), from a series showing partial auriculoventricular heart block with prolonged P-R interval.

CASE 2.—J. P. was an unmarried, white laborer. His family history was recorded as negative for goiter, rheumatism, and heart disease. At 15 years of age, he developed vague backaches which lasted for a period of two months. On entrance into the Cook County Hospital he presented the typical findings of exophthalmic goiter, with a basal metabolic rate of plus 35 per cent. He was suspected of having aortic valvulitis because of an aortic systolic murmur.

Soon after admission the patient developed acute pharyngitis, with a rise of temperature to 103° F., a leucocytosis of 12,000, and marked prostration. Joint manifestations were mild. Serial electrocardiograms showed a variable prolongation of the P-R interval, dropped beats, and complete A-V block. The variable heart block persisted throughout a two-month period and never was discovered again, though frequent electrocardiograms were taken. The basal metabolic rate rose rapidly to plus 85 per cent, and remained above plus 65 per cent for several months. During this time definite findings of aortic stenosis, and, later, mitral stenosis, appeared, with increase in size of the heart and change in its shape in the roent-

genogram. In this same period, rest in bed, sedatives, large and small doses of Lugol's solution, and roentgenotherapy failed to reduce his basal metabolism substantially or improve his condition generally. Finally, hemithyroidectomy was performed, and, later, the remainder of the gland was removed.

This patient was followed for a period of three years after thyroidectomy. The metabolic level remained normal. He still presented the findings of mitral and aortic valvular disease.

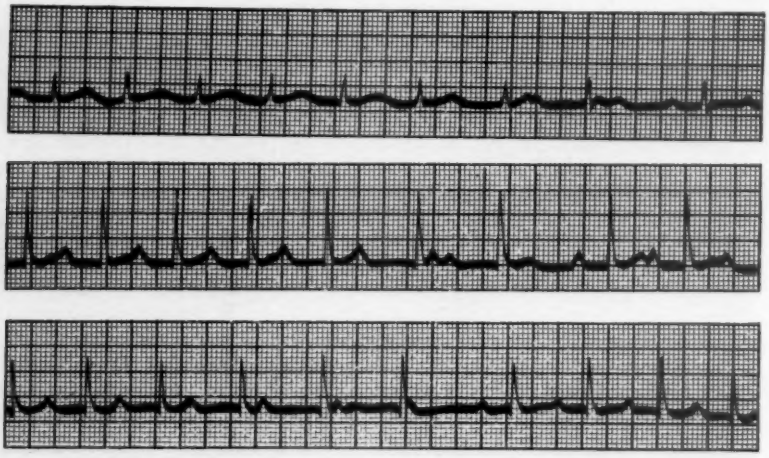

Fig. 2.—Electrocardiogram in Case 2 (J. P.), from a series showing partial auriculoventricular heart block with Wenckebach periods.

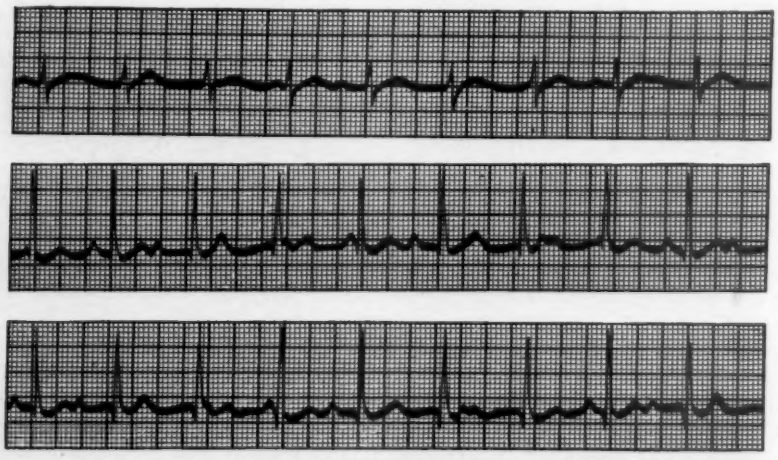

Fig. 3.—Electrocardiogram in Case 2 (J. P.), from a series showing complete auriculoventricular heart block.

CASE 3.—A. M. was a white, unmarried cook, 22 years of age. His family history was significant from the standpoint of rheumatism, as two sisters had had rheumatic fever and one of them had succumbed to rheumatic heart disease. When 4 years old the patient developed acute rheumatic fever, after frequent attacks of acute upper respiratory infections. When he was 7 years old a tonsillectomy was performed. On entrance to the Cook County Hospital he presented the typical picture of exophthalmic goiter, with a basal metabolic rate of plus 30 per cent. He

had mitral stenosis and insufficiency. One electrocardiogram showed a P-R interval of 0.28 sec. After the administration of iodides his basal metabolic rate dropped to plus 14 per cent, and subtotal thyroidectomy was performed.

This patient was readmitted to the hospital on our service two years later. At this time he showed no clinical evidence of hyperthyroidism, and had a basal metabolic rate of plus 4 per cent. He showed the characteristic findings of mitral stenosis. The electrocardiogram showed prolongation of the P-R interval with occasional dropped beats. Frequent electrocardiograms showed that the degree of block was variable and the P-R interval occasionally normal.

Four years afterward, the patient was observed when he contracted a primary syphilitic lesion followed by a secondary rash. The cardiac findings were those of mitral stenosis and insufficiency, with prolongation of the P-R interval and occasional dropped beats.

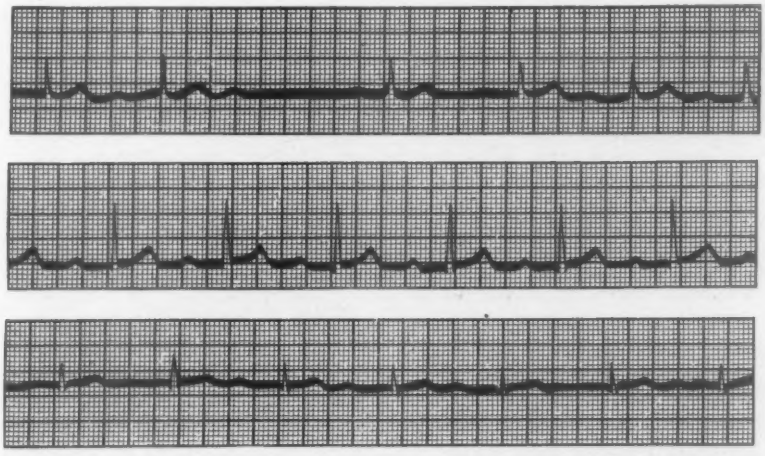

Fig. 4.—Electrocardiogram in Case 3 (A. M.), from a series showing partial auriculoventricular heart block with prolonged P-R intervals and dropped beats.

CASE 4.—L. P. was a white, unmarried waiter, 28 years of age. His family history was negative for goiter, rheumatic fever, and heart disease. When 19 years old he contracted typhoid fever. He developed acute rheumatic fever when he was 21. On entrance into the Cook County Hospital he presented the typical picture of exophthalmic goiter (basal metabolic rate, plus 55 per cent). The cardiac findings were characteristic of mitral stenosis. On admission the patient had pharyngitis, with prostration and vague joint distress, but no redness or swelling of the joints. The temperature range was from 98.2° F. to 101.4° F. The pulse rate was 100 to 140 per minute. The leucocyte count was 23,200. Electrocardiograms showed a first degree block (P-R interval, 0.24 sec.) which persisted for two weeks. After one month of iodine therapy, the basal metabolic rate was lowered to plus 16 per cent and thyroidectomy was performed.

This patient was followed for a period of one month after thyroidectomy. The basal metabolic rate remained normal. He still presented the findings of valvular heart disease.

DISCUSSION

In reviewing the literature one is able to find a number of case reports of heart block as a complication of hyperthyroidism. The majority of opinions appear to be against considering the thyroid intox-

ication as a causative factor in the production of the block. Infection has been suggested frequently as a probable cause and has been found in some cases at autopsy. Further review shows that rheumatic heart disease may also complicate hyperthyroidism. The possibility, however, that the heart block complicating hyperthyroidism may be due to acute rheumatic carditis has not been proved, although it is recognized that one of the most common causes of transient heart block (excluding digitalis) is acute rheumatic infection. The patients in this report illustrate this relationship.

All of these patients presented the classical picture of exophthalmic goiter. They had exophthalmos, diffusely enlarged thyroid glands with an audible bruit, tremor of the hands, and emotional instability. In all of them the basal metabolic rates were elevated abnormally. After thyroidectomy the symptoms of hyperthyroidism subsided, and the basal metabolic rates returned to normal and remained so.

They all presented evidence of valvular heart disease, three with mitral lesions and one with aortic and mitral involvement. The best evidence for active cardiac infection was the actual development of valvular disease in Case 2. Other evidence was the occurrence of sore throats, leucocytosis, slight fever, and joint pains.

The occurrence of heart block, when correlated with the complete clinical picture, constitutes further evidence of active rheumatic carditis. None of these patients received digitalis in any form. The actual explanation of the sequence of events depends upon an analysis of many cases of many types, each contributing corroborating evidence.

It would appear that hyperthyroidism may develop at any time in the course of a rheumatic cardiac syndrome. In Cases 1 and 4, in which there had been a childhood rheumatic infection, the onset of hyperthyroidism appeared to coincide with an exacerbation of the rheumatic carditis. In Case 2 the rheumatic and hyperthyroid syndromes seemed to have begun at about the same time. In other patients not included in this series, hyperthyroidism developed long after the acute rheumatic carditis subsided.

The heart block appears to be dependent upon the rheumatic infection and unrelated to the hyperthyroidism. Thus, in Case 2, the block disappeared two months after the onset of the pharyngitis and never reappeared, even though the hyperthyroidism persisted six months longer. In Case 3, block was present before operation during active hyperthyroidism and was known to have persisted four years after operation in varying degrees, presumably changing with the rheumatic state. In Case 4, the heart block stopped before thyroidectomy was performed, and in Case 1 the block disappeared after the operation. The absence of correlation between the cessation of the block and the termination of the hyperthyroid state would seem to sustain the contention that the heart block is not caused by the hyperthyroidism. The

course and variability of the heart block are similar in rheumatic carditis without the complicating element of hyperthyroidism. It may well be reiterated that the diagnosis of the heart block can be made definite only by electrocardiographic examination. Routine stethoscopic examinations will seldom disclose minor degrees of block. It has been found that serial electrocardiograms are necessary to detect this complication.

Observation of these patients over a long period permits the conclusion that the hyperthyroidism is a transient episode in the course of rheumatic heart disease, with heart block as a complication at that particular time. It would appear that infections, particularly of the rheumatic type, exert an unfavorable influence upon the hyperthyroidism. Apparently, however, the hyperthyroid state does not appreciably aggravate the cardiac infection. The temperature curves were comparatively low. The general condition was better than might be expected in the average rheumatic patient. In the four patients reported the manifestations of the disease in the joints were mild. In other patients, marked swelling and redness of the joints have been observed, and two patients have developed erythema nodosum.

SUMMARY

1. Four cases of exophthalmic goiter, acute rheumatic carditis, and heart block have been observed and reported.

2. It would appear that the hyperthyroidism is an episode in the course of the rheumatic heart disease, with heart block as an incidental complication.

3. Active infection of the rheumatic type seems to increase the severity of the hyperthyroidism.

4. The hyperthyroidism, conversely, apparently enables the patient to withstand the rheumatic infection better.

5. In exophthalmic goiter, heart block as a manifestation of acute carditis will be found more frequently if serial electrocardiograms are taken.

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In Memoriam

LOUIS GROSS
1895-1937

Louis Gross was born in Montreal, Canada, on May 5, 1895. He entered the Medical School of McGill University in September, 1911, after graduation from the Montreal High School. During the course in medicine he won honors for extracurricular studies and led his class in the aggregate for the five years, for which he received the Holmes Gold Medal, the highest honor which can be won by an undergraduate in medicine at McGill University.

Louis Gross

He decided at once upon an academic career, with research as the main object. As Douglas Fellow in Pathology, he spent the next five years in the Department of Pathology at the Medical School of McGill University, under the direction of Professor Horst Oertel. The major part of his time was devoted to research on the circulation of kidneys and heart. The monograph which he published in 1921 on the Blood Supply to the Heart is a classic, and will remain always as a monument to the industry and unusual ability of this remarkable young man.

Versatility was an outstanding characteristic of Louis Gross, and even in this respect he was unusual, because he excelled in everything he undertook to learn or do. As a musician and artist he was superior

to the average amateur and would have been successful as a professional had he chosen either of these fields as a career. His ingenuity and natural inventive ability helped him greatly in his later work. He was given a scholarship to induce him to continue his study of sculpture abroad, but it did not tempt him to abandon medicine. He did go abroad, but to do medical research and to broaden his basic knowledge of medicine. From 1921 to 1923, he was in London, England, first with Sir Arthur Keith, at the Royal College of Surgeons, and then, as a Beit Memorial Fellow, at University College, where he completed a valuable study on the effect of vitamin B_1 deficiency on the movements of the rat's intestine in vivo and in vitro. To acquire more knowledge of bacteriology, he spent the next year in the research department of the Board of Health under the direction of Dr. William H. Parke. After a short period as Director of Laboratories at the Brownsville and East New York Hospital, he became, in 1925, Associate Pathologist at Mount Sinai Hospital, in New York. In 1928, at the age of thirty-two years, he was appointed Director of Laboratories at Mount Sinai Hospital, in New York, with which institution he remained associated, in this position, until his death.

Although his administrative duties were heavy, yet he managed to find time almost every day for the pursuit of his own researches. Until about three years before his death, his work involved mainly the application of his knowledge of morbid morphology and of bacteriology. His contributions to our knowledge of rheumatic heart disease and coronary disease will remain permanent milestones in the history of these subjects. In recent years he began to apply experimental methods to his study of myocardial disease and of diseases of the circulatory system in general. His remarkable ingenuity asserted itself, and at once his work bore fruit. In 1937 he received medals from the American Medical Association and from the Canadian Medical Association when he demonstrated the results of what he considered only preliminary studies. Contributions of the greatest value to this field of medicine were undoubtedly prevented by his tragic and untimely death on Oct. 17, 1937. He was an outstanding student, an honest, careful, critical investigator, a great teacher, and a stimulating, brilliant lecturer.

I realize that no one who has read so far and who did not know Louis Gross can possibly have a proper conception of this extraordinary person. Although much absorbed in his own work, yet he was greatly interested in young men who were planning a career in medicine, particularly in research, and he played a most important part in the life of many young doctors. In his laboratory he made room for many young men to do part-time research, always a great burden to the administrator of a large department. He was sternly critical of the results obtained by these men, and did not permit publication of any study which, in his opinion, would not stand the test of time. The high quality of the

publications which appeared during his tenure of office is directly attributable to him. Above all else he was a warm-hearted, devoted, sincere friend to all whom he considered worthy of his friendship.

His associates and collaborators learned much from him and greatly enjoyed working with him. His aim was always the truth and not the credit. The matter of credit, especially for himself, was always of secondary importance to credit to the Institution and to his associates. The smallest contribution to a study by a part-time worker was always given full and frequently disproportionate recognition. He was an indefatigable worker, derived much pleasure from his work, and had such a buoyant, cheerful disposition that to collaborate with him was an enjoyable experience. He gave freely and generously of himself to those whom he trusted, admired, and loved, and he left behind him a host of dear friends who mourn his loss and in whose memory he will remain until their own death.

Harry Goldblatt.

Department of Reviews and Abstracts

Selected Abstracts

Grossman, Edward B., and Williams, John R.: Relation of Age to Renal Pressor Substance. Arch. Int. Med. 62: 799, 1938.

Injection of extracts containing renal pressor substance (renin) into rats of various ages showed the least rise in blood pressure in the youngest rats and the greatest rise in the oldest. On the other hand, the youngest rats had the most pressor substance in their own kidneys, and the oldest rats had the least.

The experiments suggest a possible relation between the increased sensitivity of senile rats to renal pressor substance and the tendency of elderly persons to show hypertension. However, it is concluded that no convincing evidence of such a relation exists at present.

NAIDE.

Fatherree, Thomas J., and Allen, Edgar V.: Sympathetic Vasodilator Fibers in the Upper and Lower Extremities: Observations Concerning the Mechanism of Indirect Vasodilatation Induced by Heat. Arch. Int. Med. 62: 1015, 1938.

The mechanism of indirect vasodilatation was investigated, and experiments were carried out to determine the presence of sympathetic vasodilator nerves in the upper and lower extremities of man.

It was shown that indirect vasodilatation induced by warming an extremity depends on the return of the blood from the warmed extremity to the general circulation. It was shown further that the occurrence of indirect vasodilatation in a digit depends on the integrity of its sympathetic nerve supply.

Evidence was obtained in favor of the view that there are sympathetic vasodilator nerves in the upper and lower extremities in man.

AUTHORS.

Boylston, G. A., McEwen, E. G., and Ivy, A. C.: A Pressor Substance Is Not Present in the Perfusate of Ischemic Kidneys. Proc. Soc. Exper. Biol. and Med. 39: 559, 1938.

Experiments have been carried out to determine whether or not the perfusate of ischemic kidneys of hypertensive dogs contains a pressor substance in significant amounts. Hypertension was produced in dogs by unilateral constriction of the renal artery and explanting the kidney into the flank. In one group of dogs after four days the explanted kidney was removed and perfused with warm Locke's solution for from twenty to sixty minutes. Dogs were used as assay animals. The perfusate was injected into the femoral vein of the anesthetized assay animals and systolic and diastolic blood pressures were determined in the unanesthetized state with the Hamilton recording optical manometer. In a second group of dogs, the same procedure was carried out after frank hypertension had persisted for at least three months. From these experiments there was no evidence of a pressor substance in significant amounts from the ischemic kidneys of the hypertensive dogs.

HINES.

Pickering, G. W., and Prinzmetal, M.: Experimental Hypertension of Renal Origin in the Rabbit. Clin. Sc. 3: 357, 1938.

A simple method is described of making clamps of known size suitable for constricting the renal artery in the rabbit.

In the rabbit, constriction of one renal artery, the other kidney being intact, is sometimes followed by a small and transient rise of blood pressure, and usually by atrophy of the ischemic kidney.

Constriction, by suitable clamps, of both renal arteries or of the renal artery to the only functioning kidney is followed by a slow rise of arterial pressure to a level which may be nearly double the preoperative value. In such animals with hypertension, the heart is hypertrophied and the degree of hypertrophy seems to be related, though not closely, to the degree of hypertension.

AUTHORS.

Zeus, L.: Experimental Influences of Thyrotropic Hormone on the Heart. Arch. f. Kreislauf. 4: 49, 1939.

The author demonstrated a dilatation of the heart, especially the right, following thyrotropic hormone administration. This occurred in four rabbits following daily injection of 200 ME. Histologically, the changes resembled those seen with thyroxin. These consisted of an increase in connective tissue, histiocytic cell infiltration, and cloudy swelling and fatty degeneration, especially in the right ventricle. This dilatation is followed after some days by hypertrophy. The hypertrophy is predominantly in the right ventricle.

KATZ.

Hollmann, W., and Guckes, E.: The Triogram and Its Clinical Significance. Arch. f. Kreislauf. 4: 69, 1939.

A systematic description is given of the stereotriogram and triogram in various clinical conditions such as axis shift, preponderant hypertrophy, extrasystoles, and intraventricular block. The practical value of this method demands more intensive study.

KATZ.

Müller, A.: The Mechanics of Flowing Streams With Comments on Hemodynamics. II. Flow in Tubes. Part I. Reynolds' or Turbulent Flow. Arch. f. Kreislauf. 4: 105, 1939.

This is an excellent detailed mathematical treatment of the subject, including investigations by the author. The author demonstrates that the pressure gradient in turbulent flow is about three times as great as with laminary nonturbulent flow. The profile of velocity across the cross section of a tube is the same in turbulent as in nonturbulent flow. Other details cannot be briefly abstracted but require examination of the original article.

KATZ.

Maegraith, B. G., and Carleton, H. M.: Aortic Arteriosclerosis in Rabbits. J. Path. and Bact. 48: 33, 1939.

Forty-five of 144 rabbits examined exhibited macroscopic changes in the aorta. These animals had been used for many different kinds of experiments, some of which were designed to raise the systemic blood pressure. Thirty-eight animals had heightened arterial pressure and of these, fourteen exhibited arteriosclerosis. This incidence of arterial lesions is of the same order as that found in the other animals examined, namely thirty-one out of 106.

The type of lesion observed is essentially medial and resembles the changes described by certain authors resulting from excision of the carotid sinuses, the injection of adrenalin.

From these observations it would seem that the rabbit is unsuitable for experimental work on the production of arterial disease. The high incidence of aortic lesions in our rabbits suggests, however, that the rabbit community might be useful for the investigation of the origin of spontaneous arteriosclerosis.

AUTHORS.

Essex, Hiram E., Herrick, J. F., Baldes, Edward J., and Mann, Frank C.: Influence of Exercise on Blood Pressure, Pulse Rate and Coronary Blood Flow of the Dog. Am. J. Physiol. 125: 614, 1939.

A series of experiments has been done on control dogs and dogs in which thermostromuhr units had been previously applied to the coronary arteries in an effort to determine the effect of exercise on the pulse rate, blood pressure, and coronary blood flow. Each animal had been accustomed to perform work at different rates on a treadmill.

Preliminary experiments demonstrated that the presence of the coronary thermostromuhr unit had no significant effect on the electrocardiograms or blood pressure of the animals studied.

Successive increases in the rate of work produced additional rises in blood pressure which were roughly proportional to the rate of work for the individual animals in both the control and experimental groups. As a given rate of work continued, the behavior of the blood pressure varied from animal to animal. In certain experiments the blood pressure reached a maximal level early and declined; in some it remained near the maximum; while in others it continued to augment throughout the period of exercise.

The pulse rate of the dog is a less reliable index of the rate of work than the blood pressure. The maximal pulse rate with low rates of work may be as great initially as with higher rates of work.

Simultaneous records of pulse rate, blood pressure, and coronary blood flow were made during exercise. The marked increases and decreases of coronary blood flow observed with various increments and decrements of work could not be satisfactorily accounted for by changes in blood pressure alone. The change in pulse rate with exercise was usually a better criterion than the blood pressure of changes in coronary blood flow. The evidence indicates other influences as important as blood pressure in augmenting coronary blood flow when a trained dog is given successive increments in the rate of work.

AUTHORS.

Chen, K. K., Robbins, E. Brown, and Worth, Harold: The Significance of Sugar Component in the Molecule of Cardiac Glycosides. J. Am. Pharm. A. 27: 189, 1938.

The potency of five cardiac aglycones—strophanthidin, digoxigenin, digitoxigenin, calotropagenin and scillaridin A—has been carefully determined.

Each aglycone is less powerful on the heart than its parent glycoside, more pronounced in frogs than in cats. If the aglycone undergoes chemical changes during hydrolysis, as in the case of scillaridin A and calotropagenin, the cardiac action is reduced much further.

The emetic action of strophanthidin, digoxigenin, and digitoxigenin, on the other hand, is greater than that of cymarin, digoxin, and digitoxin, respectively, molecule for molecule. When the structure of the aglycone is modified during hydrolysis, such as calotropagenin, the emetic action is diminished, but not to the same extent as the cardiac action.

The persistence of action among the aglycones is slight; that is, they are all rapidly eliminated from the circulation. This is particularly true with digitoxigenin in contrast with digitoxin.

Digitoxigenin caused a brief initial stimulation as manifested by convulsions, followed by marked depression of the central nervous system in cats and frogs. Digitoxin has no such action in corresponding doses.

AUTHORS.

Kienle, F.: Clinical and Electrocardiographic Observations on Traumatic Posterior Wall Infarct. Ztschr. f. Kreislaufforsch. 30: 674, 1938.

An injured skier came to the clinic with severe cardiac insufficiency, and clinical evidence supported by the roentgen and electrocardiographic examination indicated myocardial infarction.

KATZ.

Staemmler, M.: Does a Primary Hypertension of the Lesser Circuit Exist? (So-Called Primary Pulmonary Sclerosis.) Arch. f. Kreislaufforsch. 3: 125, 1938.

The various anatomic forms of primary pulmonary sclerosis are considered to be the result of a primary hypertension of the arterioles of the pulmonary circulation. The first change is hypertrophy of the media of the arterioles and elastica of the medium sized arteries. The other anatomic changes are secondary.

KATZ.

Kunkel, Paul, Stead, Eugene A., Jr., and Weiss, Soma: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli. J. Clin. Investigation 18: 225, 1939.

Following strong sensory stimuli, such as pinching the skin until pain is caused, or a sudden, loud noise, the forearm and calf respond in three ways: (1) by a decrease in volume after a latent period of from 3 to 9 seconds; (2) by an increase in volume after a latent period usually not exceeding 2 seconds; (3) by a biphasic response with first an increase in volume with a short latent period usually not exceeding 2 seconds, and subsequently a decrease in volume.

Reasons are stated for the belief that the decrease in volume is the result of active reflex vasoconstriction, while the increase in volume is the result of a transient increase in cardiac output and a passive distention of the vascular bed.

The sensitivity of vasomotor responses varies considerably in different persons. Variations in the same individual have been observed from time to time.

The vessels of the upper part of the body are more sensitive to physical, chemical, and nervous stimuli than those of the lower part of the body.

The blood flow induced by local heat of 43° C. is greater in the hand and foot than in the forearm and calf even when the mass of muscle present in the forearm and calf is disregarded and when the blood flow is recorded as cubic centimeters per minute per 100 sq. cm. of surface area.

Local heat of 43° C. produces nearly complete vasodilatation in the skin, but only relatively slight vasodilatation in the underlying muscles.

Exercise is a very effective stimulus for producing vasodilatation in the muscles, but not in the skin. The ability of the muscle vessels to dilate in response to exercise is not appreciably influenced by varying the external temperature between 32° and 43° C.

Pitressin, 1 c.c. intramuscularly, causes as great a decrease in blood flow in the hand and the foot at 43° C. as does epinephrine. At 43° C. it causes a moderate decrease in flow in the forearm and calf.

Neither epinephrine nor pitressin interferes with the dilatation of the muscle vessels in response to exercise or arterial occlusion.

The observation of Grant and Pearson, that unless the circulation to the hand is completely obstructed the plethysmographic method of measuring blood flow to the forearm is not accurate under all conditions, has been confirmed.

AUTHORS.

Hermann, G.: Changes in S-T and T Configuration in the Course of the Day. Arch. f. Kreislaufforsch. 3: 209, 1938.

Diurnal variation in the S-T segment and the T wave occurred in twenty out of forty-seven patients with hypertension, coronary sclerosis, and angina pectoris. These patients were examined, and it was found that these variations repeat themselves on successive days. The author concludes that these daily variations are a sign of a better outlook than their absence.

KATZ.

Freund, Hugo A., and Skokolov, Raymond: Bundle Branch Block. Arch. Int. Med. 63: 318, 1939.

The entire series of electrocardiograms taken at Harper Hospital over a ten-year period were reviewed. Two hundred and ten cases of bundle branch block and intraventricular block were found. In 179 cases (85.2 per cent) the subsequent course was studied; in the remainder of the cases the patient could not be followed. Using Wilson's criteria for the diagnosis of right bundle branch block, we were able to confirm his observation that that condition is more frequent than was previously supposed. The ratio of males to females in our series was 3 to 2. The largest number of cases occurred in patients in the sixth and seventh decades. About three-fourths of the cases occurred in conjunction with arteriosclerotic heart disease. In 15 per cent of the cases there was evidence of frank coronary occlusion.

Patients for whom the diagnosis of bundle branch block is made come to the hospital for a variety of reasons. The diagnosis is practically never made or even suspected until disclosed by electrocardiographic evidence. Consequently, these patients first present themselves with a previous history ranging from good health to complete disability. Frequently evidence of bundle branch block is discovered in the electrocardiogram of a patient who has no other signs of cardiac disease. In such cases signs or symptoms of cardiac disease may never develop. On the other hand, our records reveal repeated electrocardiograms in cases in which bundle branch lesions suddenly developed and death occurred in a short time.

There is no "clinical picture" of bundle branch block. Although bundle branch block may be discovered in conjunction with what is to all appearances a normal or near normal heart, it is most frequently associated with some degree of cardiovascular disease. Statistics in this regard do not show the absolute facts, because the taking of electrocardiograms is not a routine procedure and in many cases the condition is not discovered at its inception.

In general, it may be said that bundle branch block is most frequently found in conjunction with definite heart disease aside from the bundle lesion. Consequently the prognosis in cases of bundle branch block is at best no better that it is in cases of any form of myocardial disease. How much hazard accrues from the bundle branch block is difficult to estimate. In spite of the fact that a majority of the cases occur in aged persons and in patients suffering from cardiac disease, a fair percentage of patients live for a surprising length of time and without great discomfort.

The most important factors to be considered in determining the prognosis are the general condition of the patient and the physical signs of cardiac damage. Patients who are in good condition and show little or no signs of cardiac embarrassment are not as a rule in immediate danger. Those who are suffering from other degenerative

disease and present findings of myocardial disease, such as cardiac enlargement, cardiac arrhythmia, dyspnea, and peripheral edema, suffer seriously from a bundle branch lesion. Gallop rhythm is an ominous prognostic sign. In cases in which bundle branch block is associated with frank coronary thrombosis, the patients are usually destined to early death.

The larger percentage of patients die within the first year after the discovery of the lesion. Those who survive this first year stand an excellent chance of carrying on for a relatively longer time.

These patients with right bundle branch block lived slightly longer than those with a lesion on the left side. Patients with so-called intraventricular block had a poorer life expectancy than those with complete bundle branch block. This study did not include cases in which there was a minor degree of intraventricular block.

The aged patients seemed to withstand the ill effects of bundle branch block as well as did the younger patients.

When bundle branch block was associated with syphilitic heart disease, the prognosis was poor. Patients with bundle branch block secondary to thyroid or congenital heart disease did much better than the average. The rheumatic and arteriosclerotic patients fared about equally well, the prognosis ranking between the two extremes just cited.

Females, in general, lived longer than males with this lesion. Private and charity patients showed no outstanding differences.

AUTHORS.

Kienle, F.: Correlation of Electrocardiographic and Morphological Studies in the Differentiation of Cardiac Damage, Hypertrophy and Axis Deviation. Arch. f. Kreislauf. **4**: 19, 1939.

This is a report of seven autopsied cases carefully examined histologically. In six cases of left coronary insufficiency, the electrocardiogram showed S-T depressed in Lead I and sometimes in Lead II. In five of these there was histologic evidence of the coronary insufficiency in the form of distinct scars or fresh infarcts in the left, but not the right, ventricle.

KATZ.

Kamberg, J. A. M.: Changes in Heart Muscle in Coronary Insufficiency (An Anatomo-Clinico-Electrocardiographic Study). Arch. f. Kreislaufforsch. **3**: 340, 1938.

This is a monograph of over seventy pages. The first part is a critical assay of the theoretical aspects of the subject including a discussion of anatomy and dynamics as it pertains to the problem of coronary insufficiency. This is followed by a discussion of pathologic changes and of the etiology of heart failure. The author then summarizes his experiences based on 300 autopsies of healed heart muscle infarcts and coronary disease. This is supplemented by studies of sixty-three ward patients having coronary sclerosis with or without hypertension or valvular defects and syphilitic coronary mouth closure.

KATZ.

Levine, Samuel A.: Angina Pectoris and Its Relation to Coronary Artery Disease. New England J. Med. **219**: 743, 1938.

"Angina pectoris" is a useful term, but should be confined to designate patients suffering from a peculiar type of distress in the chest or neighboring structures who are liable to sudden, unexpected death. The diagnosis depends almost entirely on the proper interpretation of symptoms. For this reason, direct inquiry is often

necessary in order to avoid overlooking many cases of angina. The characteristic complaints may be so mild or may have occurred so long ago that they are not mentioned by the patient. This accounts for the frequent occurrence of sudden death in patients with cardiac illness in whose cases the diagnosis of angina was overlooked.

Except for a few conditions like paroxysmal rapid heart action, hyperthyroidism, anemia, and aortic valvular disease, angina is always associated with pathologic changes in the coronary arteries. Even in the conditions just mentioned these vessels are often involved.

Angina pectoris is not synonymous with sclerosis of the coronary arteries, for the former is a functional state and the latter is a structural one. The latter may be present in the absence of the former.

Spontaneous attacks of angina may involve factors, especially neurogenic ones, different from those which obtain when attacks are reproduced deliberately by performing functional tests such as the two-step test.

AUTHOR.

Whitehill, M. Richard, Longcope, Warfield T., and Williams, Russell: The Occurrence and Significance of Myocardial Failure in Acute Hemorrhagic Nephritis. Bull. Johns Hopkins Hosp. **64**: 83, 1939.

From a study of 138 patients, mostly young adults, suffering from the form of acute hemorrhagic nephritis that follows directly upon an active infection due usually to hemolytic streptococci, it has been observed that circulatory insufficiency often forms an integral part of the illness. It is characteristic that evidences of circulatory failure may appear at the onset or during the first few days of the disease. These manifest themselves as dyspnea which may become paroxysmal or progress to orthopnea, by enlargement of the heart, accompanied by alterations in the impulses and sounds, by elevation of venous pressure, and by enlargement of the liver.

The circulatory failure may well lead to an increase of subcutaneous edema, or to cerebral or pulmonary edema, and may produce other deleterious effects such as interference with the function of the injured kidneys. These conditions are uncommon in mild attacks of nephritis, frequent in moderately severe attacks, and present in the majority of cases of severe acute nephritis. The use of digitalis in full doses has seemed to benefit some of these patients with severe circulatory failure.

AUTHORS.

Thomas, Caroline Bedell, and France, Richard: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever. Bull. Johns Hopkins Hosp. **64**: 67, 1939.

Sulfanilamide was given continuously during the course of two winters to thirty individuals with recent history of acute rheumatic fever. The drug was taken daily over a seven months' period in a dosage of 15 to 20 grains without ill effects. None of the patients had a major attack of acute rheumatic fever or an acute beta hemolytic streptococcal infection while taking sulfanilamide. Of thirty control patients, four developed five major attacks of rheumatic fever during the same period, one was hospitalized because of an acute beta hemolytic streptococcal infection, and three others had acute illnesses which might have been of a rheumatic character. It is recognized that the group studied is too small to permit definite conclusions concerning the efficacy of sulfanilamide in preventing attacks of acute rheumatic fever, but the results are encouraging and warrant further studies along this line.

AUTHORS.

Coburn, Alvin F., and Moore, Lucile V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, With Especial Reference to Rheumatic Fever. J. Clin. Investigation **18**: 147, 1939.

Sulfanilamide appeared to give complete protection to a colony of guinea pigs against spontaneous lymphadenitis with Group C hemolytic streptococcus. Sulfanilamide seemed to protect about two-thirds of the animals which received a large dose of the same organisms intranasally, and modified the disease in the remaining third.

During the course of the study there were no drug symptoms, no frank streptococcal infections, and no attacks of acute rheumatism. Sulfanilamide did not prevent the occurrence of a number of "common colds," one pneumococcus ear infection, and one severe bronchitis of unknown etiology.

These observations showed that quiescent rheumatic subjects can be maintained for many months at a high blood sulfanilamide level without demonstrable ill effects. These patients were visited by their families, were exposed to 2 patients with streptococcal infections who were introduced into The Pelhman Home, and lived in close proximity with a carrier of hemolytic streptococcus and with six nonmedicated patients who had positive cultures or rheumatic activity or both at some time during the experiment. Only one of the twenty-six medicated patients contracted an infection with hemolytic streptococcus in the throat flora. Twenty-five highly susceptible rheumatic children were maintained in good health throughout the winter and spring months.

This group of twenty patients appeared to escape streptococcal respiratory infection although a number of them had "common colds" and one developed measles. They also escaped clinical evidence of rheumatic fever. Their freedom from rheumatic activity can best be visualized from the record of their sedimentation rates, given in Table VII.

AUTHOR.

Gauld, Ross L., Ciocco, Antonio, and Read, Frances E. M.: Further Observations on the Occurrence of Rheumatic Manifestations in the Families of Rheumatic Patients. J. Clin. Investigation **18**: 213, 1939.

Facts have been presented relative to the high incidence of rheumatic disease in the families of ninety-six rheumatic children. The percentage of persons with a rheumatic history, who had parents with a similar history, was found to be consistent in two generations of these families and was 3.7 times as high as that found in a group of control families.

The offspring of the grandparents of the rheumatic and control index cases were studied to see if any relationship was present between the type of mating with respect to rheumatic disease and the percentage of children who were rheumatic. When one or both parents had a history of rheumatic manifestations, a greater percentage of the offspring was rheumatic than was found in the offspring of parents who gave no history of rheumatic disease.

The percentage of female offspring of rheumatic mothers who had rheumatic manifestations was found to be almost twice as high as in the male offspring of these mothers.

A greater percentage of persons with rheumatic disease was found among the maternal aunts and uncles than was found among the paternal aunts and uncles of rheumatic index cases.

These findings suggest that hereditary constitution may play a role in the predisposition to this disease. The evidence here presented does not, however, exclude the possibility that infection plays an important role, and that exposure may be the predominating factor.

AUTHORS.

Kissane, Ray W., Koons, Ruth A., and Mahanna, Donald L.: The Role of Syphilis in Coronary Artery Sclerosis, Occlusion and Angina Pectoris. Urol. & Cutan. Rev. 63: 3, 1939.

A review of 5,859 autopsies, divided into syphilitic and nonsyphilitic groups, revealed the incidence of coronary artery sclerosis in the syphilitic group to be approximately four times greater than that of the nonsyphilitic group. However, this cannot be considered as evidence that syphilis is an important secondary factor in the production of coronary artery disease.

The incidence of coronary artery occlusion in the syphilitic group as compared to the nonsyphilitic group was slightly greater but was considered coincidental because of the small number of syphilitic cases against the much greater number of nonsyphilitic cases.

A study of 3,329 clinical cases, divided into syphilitic and nonsyphilitic groups, revealed the incidence of angina pectoris to be almost ten times greater in the nonsyphilitic group than in the syphilitic group.

It is evident that syphilis is not a primary or secondary factor in the production of coronary artery occlusion or angina pectoris.

AUTHORS.

Stern, Neuton S.: Arteriosclerosis: Considerations as to Etiology. Southern Med. J. 32: 370, 1939.

There are reasons for believing that vasa vasorum in the walls of arteries extend through the media and the intima as well as the adventitia. The occlusion and inflammation of the vasa vasorum cause the lesions described as arteriosclerosis. The occlusion may be caused by small particles, such as emboli, clumps of bacteria, fibrin particles, fat globules, clumps of white blood cells, phagocytes, pigments, cell detritus, and nuclear fragments. In addition a number of other possible mechanisms of blocking of the lumens of vasa vasorum are discussed, particularly with reference to diabetes mellitus, obesity, hypertension, and old age. In this manner the author attempts to unify the various theories which have been advanced to explain the development of arteriosclerosis.

NAIDE.

Rook, A. F., and Dawson, D. J.: Hypotension and Flying. The Lancet 2: 1503, 1938.

Hypotension may be said to be present when the systolic blood pressure is below 110 mm. Hg or the diastolic below 70 mm. Hg. Moderate grades of hypotension are considered to be present if the systolic level is between 110 and 100 mm. Hg or the diastolic between 70 and 60 mm. Hg; severe grades when the systolic pressure is below 100 mm. Hg or the diastolic below 60 mm. Hg.

Hypotension is sometimes accompanied by symptoms, such as postural giddiness, and, when so associated, is an absolute bar to all flying. An isolated finding of a severe grade of hypotension is compatible with good health but always calls for considerable caution when assessing for flying duties.

Hypotensive persons may be divided into two ill-defined groups: (a) occasional hypotensives, and (b) persistent hypotensives. (a) Occasional hypotension is not uncommon and is found in a large proportion of young adults when repeated examinations are made. As an isolated finding moderate grades are of little importance so far as flying is concerned. (b) Persistent hypotension is comparatively rare. It is not necessarily, or even usually, permanent but lasts only for a variable period. It may be associated with symptoms of hypotension or with some underlying disease, in which case it is a bar to flying. It is, however, compatible with good health, and then piloting duties may be permitted.

It is probable that the ability of the cardiovascular system to withstand centrifugal effects during flight depends largely on its power to react rapidly to stress. This power is as necessary for the person with normal blood pressure as for the hypotensive.

AUTHORS.

Westcott, F. H., and Wright, I. S.: Tobacco Allergy and Thromboangiitis Obliterans. J. Allergy **9**: 555, 1938.

The authors found no evidence suggesting that thromboangiitis obliterans was related to tobacco sensitivity. Skin tests and reactions were no more frequent in a group of patients with this condition than in a control group.

MCCULLOCH.

Mendlowitz, Milton: Some Observations on Clubbed Fingers. Clin. Sc. **3**: 387, 1938.

The response of the blood vessels in clubbed fingers to environmental temperature changes is qualitatively normal and the maximum heat eliminations of the hands of patients with clubbed fingers are within normal limits.

The maximum heat elimination and hence the blood flow of the distal phalanges of clubbed fingers secondary to lung or congenital heart disease are usually increased.

The digital arterial pressure is increased and the brachial-digital arterial pressure gradient decreased in clubbing secondary to lung or congenital heart disease. In hereditary clubbing these pressures and gradients are normal.

The blood flow of the unilaterally clubbed finger tip, as indicated by maximum heat elimination may be increased or decreased. No significant change was found in the blood pressure gradient except for a bilateral decrease in a case interpreted to be bilateral clubbing with acceleration of the process in the fingers of one hand due to a sympathetic nerve lesion.

AUTHOR.

Homans, John: Varieties of Thrombophlebitis of the Limbs. Their Origin, Course and Treatment. Am. J. Surg. **44**: 3, 1939.

This is an excellent account of the known varieties of thrombophlebitis. The factors involved in the development of thrombophlebitis are mentioned. Each type is described and treatment is discussed.

NAIDE.

Weir, David R.: Polyarteritis Nodosa. Am. J. Path. **15**: 79, 1939.

A case of polyarteritis nodosa is reported with clinical and pathologic findings. A number of unusual features were found in the gross and microscopic examination. These unusual features are: (1) Evidence that the primary lesion occurred in the intima and inner layers of the media and progressed outward through the wall to the adventitia; (2) occurrence of all stages of arteritis from the earliest acute to the healed, but restriction of the lesions in each individual organ to roughly one stage; (3) remarkable parenchymatous lesions of the lungs and spleen; and (4) resemblance of the gross autopsy findings to widespread tuberculosis. In no instance did the disease process involve arteries greater than 1.5 mm. in diameter.

The findings in this case and evidence presented by others make it reasonably certain that the lesions are not primarily periarterial. The author agrees with the suggestion of others that the name polyarteritis nodosa be substituted for the misnomer, periarteritis nodosa.

NAIDE.

Burwell, C. Sidney, Strayhorn, W. David, Flickinger, Don, Corlette, Marvin B., Bowerman, Earl P., and Kennedy, J. Allen: Circulation During Pregnancy. Arch. Int. Med. **62**: 979, 1938.

Observations on the pulse rate, the systemic blood pressure, the vital capacity, the arteriovenous difference, and the cardiac output made for four women during the course of pregnancy, and in the puerperium, may be summarized as follows:

The basal pulse rate is higher during pregnancy than after delivery; the basal blood pressure (particularly the diastolic phase) is lower during pregnancy than after its termination.

The cardiac output is increased, by as much as 50 per cent or even more, during the period of maximum increase. This increase is usually demonstrable by the third or fourth month. In the last weeks of pregnancy there is a fall in the cardiac output toward normal, and after delivery it is within the limits usual for nonpregnant women.

The increase in output is greater in proportion than the increase in oxygen consumption; therefore the arteriovenous oxygen difference is diminished.

The observations on venous pressures in pregnant women may be summarized as follows:

Venous pressures are nearly the same in the arm and in the leg in supine persons, both normal persons and patients with central obstruction, leading to general elevation of the venous pressure.

Difference between these pressures may exist when there is a condition affecting the venous return from a part of the body, such as a mediastinal or pelvic tumor.

In pregnant women by the beginning of the second trimester the pressure in the leg is notably higher than that in the arm. It continues high throughout pregnancy, but after delivery it is found to be no higher than the pressure in the arm.

These observations on animals may be summarized as follows:

Pressure in the femoral veins is elevated during pregnancy; that in the uterine veins is higher than that in the femoral veins.

These changes are not due to an increase in general intra-abdominal pressure.

The femoral pressure may be lowered if the uterus is elevated and supported; it may be further lowered if the uterus is excised and its vascular connections are severed.

Blood from the veins draining the pregnant uterus tends to exhibit an oxygen content that is high in relation to that of the blood in the right ventricle.

The demonstrated phenomena of the circulation in pregnant women and pregnant animals, plus the available knowledge concerning the structure of the placenta, lead to the conclusion that the changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) an arteriovenous leak through the placenta and (2) an obstruction to venous return by the enlarged uterus.

AUTHORS.

Mayer, Karol: An X-ray Inquiry Into the Genesis of the Current of Venous Blood and Lymph. Radiology **32**: 275, 1939.

The arterial pulse in any organ is transmitted to adjacent tissues. With every beat the suddenly growing pressure produces greater rigidity in the region surrounding the venous and lymphatic vessels. Since the direction of least resistance is toward the heart, the increased pressure on the veins and lymphatics, with each beat, causes a movement of blood and lymph in the direction of the heart.

NAIDE.

McGuire, Johnson, Shore, Rose, Hauenstein, Virgil, and Goldman, Fred: Relation of Cardiac Output to Congestive Heart Failure. Arch. Int. Med. 63: 290, 1939.

In nineteen of twenty cases of congestive heart failure the cardiac output was subnormal, the mean value being 1.52 ± 0.06 liters per square meter per minute, while in control cases the mean was 2.16 ± 0.03 liters.

In the groups of patients with congestive failure of varying severity there was a trend toward reduction of cardiac output with the severer manifestations of failure.

AUTHORS.

Heim de Balsac, R.: Anatomical-Radiological Study of the Thoracic Aorta. Presse méd. 45: 1749, 1937.

This is a study of the aorta by contrast media injected post mortem and by casts. The changes determined by age and by the different shapes of the thorax are described in detail.

JENSEN.

Stevenson, C. A.: The Use of Roentgen Therapy in the Carotid Sinus Syndrome. Radiology 32: 209, 1939.

Five patients with carotid sinus syndrome received roentgen therapy, with definite prophylactic value in each.

NAIDE.

Smithwick, Reginald H.: Medical Progress: Surgery of the Sympathetic Nervous System. N. Eng. J. Med. 220: 475, 1939.

This is a review of the applications of surgery of the sympathetic nervous system to peripheral vascular disease, anterior poliomyelitis, hyperhidrosis, Hirschsprung's disease, essential hypertension, pain in the head, face and arms, causalgia, angina pectoris, abdominal visceral pain, and genitourinary tract pain.

NAIDE.

Wald, Maurice H., Lindberg, Howard A., and Barker, M. Herbert: The Toxic Manifestations of the Thiocyanates. J. A. M. A. 112: 1120, 1939.

After ten years' experience with cyanate therapy in hypertension, carefully controlled by determination of the blood content of the drug, the authors present an analysis of the literature on the subject of its toxicity and make suggestions for the clinical guidance to the toxicology and therapeutics of this salt. The beneficial action of thiocyanates in cases of hypertension depends in part on their peculiar toxicology. An attempt is made to differentiate those toxic signs and symptoms which might occur normally in the hypertensive person from those which occur directly as a result of cyanate intoxication.

Symptoms which appear during thiocyanate therapy must be interpreted in the light of the level of the blood cyanates. Without blood cyanate determinations, this drug should not be used.

NAIDE.

Book Review

THE HEART IN PREGNANCY: By Julius Jensen, M.D., Ph.D. (in Medicine), University of Minnesota, M.R.C.S (England), L.R.C.P. (London). Assistant Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital; Physician to St. Louis Maternity Hospital and St. Louis City Hospital. 371 pages, $5.50. St. Louis, 1938, The C. V. Mosby Company.

There has been a great need for some such book as this on the subject of heart disease and pregnancy, to bring together the many scattered observations which bear on the physiology of the circulation of the pregnant woman and the effects of pregnancy upon the patient with heart disease. One might wish at times that the references to the literature did not extend back beyond the beginnings of our present concepts of heart disease, though perhaps there may be value in calling attention to the abandonment of former concepts, thus teaching us to be more critical of the ones to which we now hold. Most of the older literature cited has little more than historical interest, and serves at times to obscure the more modern, and, we hope, more firmly grounded observations. The review of the modern literature is very well conducted, and the opinions of the different observers well correlated. The author's critical attitude is conservative and tends to point out the need of further investigations and the lines along which these should be projected. His application of the statistical method to the case reports in the literature leads at times to interesting and important conclusions. Owing to the caution with which he handles the statistics, one is usually ready to agree with these conclusions. At other times the material upon which the different case reports have been based has been collected by authors with such different standards, and in hospitals with such different types of clientele, that they cannot be logically grouped to form a basis for statistical conclusions. The author is aware of this source of error and discounts its results as much as possible, but it always remains an inherent and unaccountable source of weakness in his conclusions.

The causes for the increased cardiac work during pregnancy and what is known of the mechanism whereby the heart meets these demands are discussed. When all is said and done, our knowledge on these subjects is meager. There is a profitable review of the effects of pregnancy upon the normal heart and circulation which will serve as a basis for an understanding of the changes that might be expected in a diseased heart during pregnancy. There is an interesting discussion of the frequency and importance of cardiac arrhythmia during pregnancy.

Over a third of the book is occupied with an excellent discussion of the various aspects of rheumatic heart disease which result from the advent of pregnancy and labor. The section on the diagnosis of rheumatic valvular disease seems to place much less emphasis upon the observation of physical signs than do the Criteria for the Diagnosis of Heart Disease of the New York Heart Association. The condition described as functional heart disease of pregnancy warrants special attention, for it is so rarely described in the modern obstetrical-cardiac literature as to raise a doubt as to its occurrence. The reviewer has not seen such a case. The appearance of dyspnea, tachycardia, and edema during pregnancy in a patient with heart disease cannot "always indicate that a damaged heart is becoming embarrassed," for such symptoms appear in many healthy women during pregnancy, and it is likely that they may arise in a woman with heart disease by the same mechanism as in the woman without this handicap.

There is a good discussion of the management of decompensation during pregnancy and the indications for interrupting pregnancy because of heart disease. The semirecumbent position during delivery is mentioned, but its importance is scarcely sufficiently emphasized, especially for certain patients who show a tendency to dyspnea when lying flat. Forceps and cesarean section and anesthesia receive satisfactory discussions. Cesarean section is recommended as the safest way of relieving an embarrassed heart of the strain of labor. It is interesting to read that there is "no evidence that lactation has done harm where compensation has been adequate," for this viewpoint is sufficiently considered by obstetricians. The effects of pregnancy upon degenerative heart disease, hypertension, congenital heart disease, kyphoscoliosis, and syphilitic heart disease are also discussed.

The bibliography occupies over fourteen pages, and, although a certain amount of this is only of historical interest, it includes all of the worth-while modern contributions of European and American authors. Such a compilation in itself is of great value to the student of the overlapping terrain of obstetrics and cardiology. Anyone who has had experience in this field or who wishes to acquire knowledge of it will find this book a most valuable source of information and reference.

HAROLD E. B. PARDEE.

Books Received

ALLGEMEINE ELECTROKARDIOGRAPHIE, Ed. 4, by Prof. Dr. Eberhard Koch, Bad-Nauheim, 1939, Theodor Steinkopff, 41 pp., 41 illustrations, RM 2.25.

ÉLECTROCARDIOGRAPHIE EXPERIMENTALE. Application à La Physio-Pathologie du Coeur Dualite du Coeur Arythmies, by Docteur E. Desomer, Paris, 1938, Masson et Cie, 142 pp., 77 illustrations, 60 francs.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

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The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

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Vol. 17 JUNE, 1939 No. 6

THE AMERICAN HEART JOURNAL

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A JOURNAL FOR THE STUDY OF THE CIRCULATION

PUBLISHED MONTHLY

UNDER THE EDITORIAL DIRECTION OF

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Vol. 17, No. 6, June, 1939. The American Heart Journal is published monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, Canada, $8.50 a year; Foreign, $9.50. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879.

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Tincture Digitalis Squibb is carefully assayed and standardized by the U. S. P. frog method to make each 1 cc. equivalent to 1.0-1.1 U. S. P. XI (International) units. Since it is in excellent demand it will, under all reasonable conditions, be found to have the correct U. S. P. strength at the time of use.

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In the use of Tincture Digitalis, accuracy is important and convenience desirable. The one-fluidounce package Tincture Digitalis Squibb provides both these features. A special dropper (included in each 1-fluidounce package) delivers drops of exactly one minim each—no more, no less. The detachable label on the carton makes it possible for the pharmacist to conveniently dispense the Tincture and the dropper as one unit. Tincture Digitalis Squibb is also available in 1-, 4-, and 16-fl. oz. and gallon bottles.

ALSO AVAILABLE

Aminophylline Squibb (Theophylline with Ethylene Diamine, U. S. P. XI) is supplied in tablets of 100 mg. (1½ gr.) each, in vials of 10 and bottles of 100 tablets. Aminophylline Powder is supplied in 10-Gm. vials and 1-oz. bottles for prescription use and for the preparation of solutions for rectal or parenteral administration. The product is useful as a coronary vasodilator, as a diuretic, as a myocardial stimulant, and as an adjunct to digitalis therapy.

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Other Squibb Digitalis Products: TABLETS DIGITALIS 1 GR. • CAPSULES DIGITALIS POWDER STANDARDIZED DIGITALIS POWDER • TABLETS DIGITALIS ¼ AND 1 CAT UNIT